

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 215/38, 241/44, 277/72, A61K 31/47, 31/495, 31/425	A2	(11) International Publication Number: WO 99/26927
		(43) International Publication Date: 3 June 1999 (03.06.99)

(21) International Application Number: PCT/US98/24833

(22) International Filing Date: 20 November 1998 (20.11.98)

(30) Priority Data:
60/066,758 21 November 1997 (21.11.97) US(63) Related by Continuation (CON) or Continuation-in-Part
(CIP) to Earlier Application
US 60/066,758 (CIP)
Filed on 21 November 1997 (21.11.97)(71) Applicant (for all designated States except US): NPS PHAR-
MACEUTICALS, INC. [US/US]; 420 Chipeta Way, Salt
Lake City, UT 84108 (US).

(72) Inventors; and

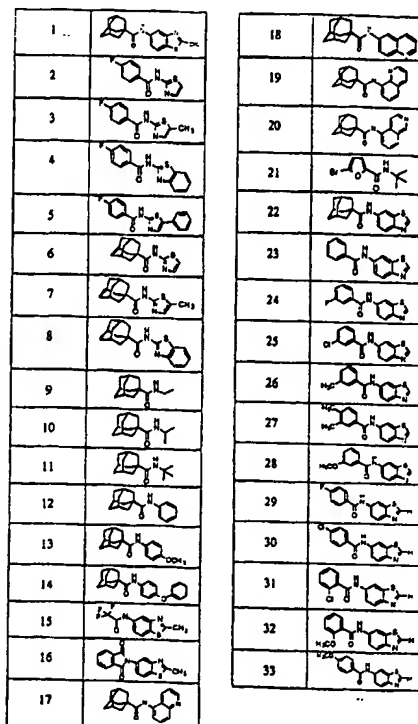
(75) Inventors/Applicants (for US only): VAN WAGENEN, Brad-
ford, C. [US/US]; 3969 South 3250 East, Salt Lake City,
UT 84124 (US). MOE, Scott, T. [US/US]; 6152 South Vine-
field Lane, Salt Lake City, UT 84121 (US). SMITH, Daryl,
L. [US/US]; 1592 East Parkridge Drive, Salt Lake City,
UT 84121 (US). SHEEHAN, Susan, M. [US/US]; 1803
East Redondo Avenue, Salt Lake City, UT 84108 (US).
SHCHERBAKOVA, Irina [RU/US]; 150 East First Av-enue, Salt Lake City, UT 84103 (US). TRAVATO, Richard
[US/US]; 4636 South 3075 East, Salt Lake City, UT 84117
(US). WALTON, Ruth [US/US]; 1348 Country Hills Drive,
Ogden, UT 84403 (US). BARMORE, Robert [US/US]; 1172
East Sunnyside Avenue, Salt Lake City, UT 84102 (US).
DELMAR, Eric, G. [US/US]; 2967 East St. Mary's Circle,
Salt Lake City, UT 84108 (US). STORMANN, Thomas, M.
[US/US]; 1327 East Harrison, Salt Lake City, UT 84105
(US).(74) Agents: BENT, Stephen, A. et al.; Foley & Lardner, Suite 500,
3000 K Street, N.W., Washington, DC 20007-5109 (US).(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR,
BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD,
GE, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM,
KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE,
CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,
NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA,
GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished
upon receipt of that report.(54) Title: METABOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS FOR TREATING CENTRAL NERVOUS SYSTEM
DISEASES

(57) Abstract

The present invention provides compounds, and pharmaceutical compositions containing those compounds, that act as antagonists at metabotropic glutamate receptors. The compounds are useful for treating neurological diseases and disorders. Methods of preparing the compounds also are disclosed.



BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

METABOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS FOR TREATING CENTRAL NERVOUS SYSTEM DISEASES**FIELD OF THE INVENTION**

The present invention provides compounds active at metabotropic glutamate receptors and that are useful for treating neurological and psychiatric diseases and disorders.

5

BACKGROUND OF THE INVENTION

Recent advances in the elucidation of the neurophysiological roles of metabotropic glutamate receptors have established these receptors as promising drug targets in the therapy of acute and chronic neurological and psychiatric disorders and diseases. However, the major challenge to the realization of this promise has been the development of metabotropic glutamate receptor subtype-selective compounds.

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system (CNS). Glutamate produces its effects on central neurons by binding to and thereby activating cell surface receptors. These receptors have been divided into two major classes, the ionotropic and metabotropic glutamate receptors, based on the structural features of the receptor proteins, the means by which the receptors transduce signals into the cell, and pharmacological profiles.

The metabotropic glutamate receptors (mGluRs) are G protein-coupled receptors that activate a variety of intracellular second messenger systems following the binding of glutamate. Activation of mGluRs in intact mammalian neurons elicits one or more of the following responses: activation of phospholipase C; increases in phosphoinositide (PI) hydrolysis; intracellular calcium release; activation of phospholipase D; activation or inhibition of adenylyl

- 2 -

cyclase: increases or decreases in the formation of cyclic adenosine monophosphate (cAMP); activation of guanylyl cyclase: increases in the formation of cyclic guanosine monophosphate (cGMP); activation of phospholipase A₂: increases in arachidonic acid release; and increases or decreases in the activity of voltage- and ligand-gated ion channels. Schoepp *et al.*, *Trends Pharmacol. Sci.* 14:13 (1993); Schoepp, *Neurochem. Int.* 24:439 (1994); Pin *et al.*, *Neuropharmacology* 34:1 (1995).

Eight distinct mGluR subtypes, termed mGluR1 through mGluR8, have been identified by molecular cloning. See, for example, Nakanishi, *Neuron* 13:1031 (1994); Pin *et al.*, *Neuropharmacology* 34:1 (1995); Knopfel *et al.*, *J. Med. Chem.* 38:1417 (1995). Further receptor diversity occurs via expression of alternatively spliced forms of certain mGluR subtypes. Pin *et al.*, *PNAS* 89:10331 (1992); Minakami *et al.*, *BBRC* 199:1136 (1994); Joly *et al.*, *J. Neurosci.* 15:3970 (1995).

Metabotropic glutamate receptor subtypes may be subdivided into three groups, Group I, Group II, and Group III mGluRs, based on amino acid sequence homology, the second messenger systems utilized by the receptors, and by their pharmacological characteristics. Nakanishi, *Neuron* 13:1031 (1994); Pin *et al.*, *Neuropharmacology* 34:1 (1995); Knopfel *et al.*, *J. Med. Chem.* 38:1417 (1995).

Group I mGluRs comprise mGluR1, mGluR5, and their alternatively spliced variants. The binding of agonists to these receptors results in the activation of phospholipase C and the subsequent mobilization of intracellular calcium. Electrophysiological measurements have been used to demonstrate these effects in, for example, *Xenopus* oocytes expressing recombinant mGluR1 receptors. See, for example Masu *et al.*, *Nature* 349:760 (1991); Pin *et al.*, *PNAS* 89:10331 (1992). Similar results have been achieved with oocytes expressing recombinant mGluR5 receptors. Abe *et al.*, *J. Biol. Chem.* 267:13361 (1992); Minakami *et al.*, *BBRC* 199:1136 (1994); Joly *et al.*, *J. Neurosci.* 15:3970 (1995). Alternatively, agonist activation of recombinant mGluR1 receptors expressed in Chinese hamster ovary (CHO) cells stimulates PI hydrolysis, cAMP formation, and arachidonic acid release as measured by standard biochemical assays. Aramori *et al.*, *Neuron* 8:757 (1992).

- 3 -

In comparison, activation of mGluR5 receptors expressed in CHO cells stimulates PI hydrolysis and subsequent intracellular calcium transients, but no stimulation of cAMP formation or arachidonic acid release is observed. Abe *et al.*, *J. Biol. Chem.* 267:13361 (1992). However, activation of mGluR5 receptors expressed in LLC-PK1 cells results in PI hydrolysis and increased cAMP formation. Joly *et al.*, *J. Neurosci.* 15:3970 (1995). The agonist potency profile for Group I mGluRs is quisqualate > glutamate = ibotenate > (2*S*,1'*S*,2'*S*)-2-carboxycyclopropylglycine (L-CCG-I) > (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid (ACPD). Quisqualate is relatively selective for Group I receptors, as compared to Group II and Group III mGluRs, but it also is a potent activator of ionotropic AMPA receptors. Pin *et al.*, *Neuropharmacology* 34:1, Knopfel *et al.*, *J. Med. Chem.* 38:1417 (1995).

The lack of subtype-specific mGluR agonists and antagonists has impeded elucidation of the physiological roles of particular mGluRs, and the mGluR-associated pathophysiological processes that affect the CNS have yet to be defined. However, work with the available non-specific agonists and antagonists has yielded some general insights about the Group I mGluRs as compared to the Group II and Group III mGluRs.

Attempts at elucidating the physiological roles of Group I mGluRs suggest that activation of these receptors elicits neuronal excitation. Various studies have demonstrated that ACPD can produce postsynaptic excitation upon application to neurons in the hippocampus, cerebral cortex, cerebellum, and thalamus, as well as other brain regions. Evidence indicates that this excitation is due to direct activation of postsynaptic mGluRs, but it also has been suggested that activation of presynaptic mGluRs occurs, resulting in increased neurotransmitter release. Baskys, *Trends Pharmacol. Sci.* 15:92 (1992); Schoepp, *Neurochem. Int.* 24:439 (1994); Pin *et al.*, *Neuropharmacology* 34:1(1995).

Pharmacological experiments implicate Group I mGluRs as the mediators of this excitatory mechanism. The effects of ACPD can be reproduced by low concentrations of quisqualate in the presence of iGluR antagonists. Hu *et al.*, *Brain Res.* 568:339 (1991); Greene *et al.*, *Eur. J. Pharmacol.* 226:279 (1992). Two phenylglycine compounds known to activate mGluR1, namely (*S*)-3-hydroxyphenylglycine ((*S*)-3HPG) and (*S*)-3,5-dihydroxyphenylglycine ((*S*)-DHPG), also produce excitation. Watkins *et al.*, *Trends Pharmacol. Sci.* 15:33

- 4 -

(1994). In addition, the excitation can be blocked by (*S*)-4-carboxyphenylglycine ((*S*)-4CPG), (*S*)-4-carboxy-3-hydroxyphenylglycine ((*S*)-4C3HPG), and (+)-alpha-methyl-4-carboxyphenylglycine ((+)-MCPG), compounds known to be mGluR1 antagonists. Eaton *et al.*, *Eur. J. Pharmacol.* 244:195 (1993); Watkins
5 *et al.*, *Trends Pharmacol. Sci.* 15:333 (1994).

Metabotropic glutamate receptors have been implicated in a number of normal processes in the mammalian CNS. Activation of mGluRs has been shown to be required for induction of hippocampal long-term potentiation and cerebellar long-term depression. Bashir *et al.*, *Nature* 363:347 (1993); Bortolotto *et al.*,
10 *Nature* 368:740 (1994); Aiba *et al.*, *Cell* 79:365 (1994); Aiba *et al.*, *Cell* 79:377 (1994). A role for mGluR activation in nociception and analgesia also has been demonstrated. Meller *et al.*, *Neuroreport* 4: 879 (1993). In addition, mGluR activation has been suggested to play a modulatory role in a variety of other normal processes including synaptic transmission, neuronal development,
15 apoptotic neuronal death, synaptic plasticity, spatial learning, olfactory memory, central control of cardiac activity, waking, motor control, and control of the vestibulo-ocular reflex. For reviews, see Nakanishi, *Neuron* 13: 1031 (1994); Pin *et al.*, *Neuropharmacology* 34:1; Knopfel *et al.*, *J. Med. Chem.* 38:1417 (1995).

20 Metabotropic glutamate receptors also have been suggested to play roles in a variety of pathophysiological processes and disease states affecting the CNS. These include stroke, head trauma, anoxic and ischemic injuries, hypoglycemia, epilepsy, and neurodegenerative diseases such as Alzheimer's disease. Schoepp *et al.*, *Trends Pharmacol. Sci.* 14:13 (1993); Cunningham *et al.*, *Life Sci.* 54:135
25 (1994); Hollman *et al.*, *Ann. Rev. Neurosci.* 17:31 (1994); Pin *et al.*, *Neuropharmacology* 34:1 (1995); Knopfel *et al.*, *J. Med. Chem.* 38:1417 (1995). Much of the pathology in these conditions is thought to be due to excessive glutamate-induced excitation of CNS neurons. Because Group I mGluRs appear to increase glutamate-mediated neuronal excitation via postsynaptic mechanisms
30 and enhanced presynaptic glutamate release, their activation probably contributes to the pathology. Accordingly, selective antagonists of Group I mGluR receptors could be therapeutically beneficial, specifically as neuroprotective agents or anticonvulsants.

- 5 -

Preliminary studies assessing therapeutic potentials with the available mGluR agonists and antagonists have yielded seemingly contradictory results. For example, it has been reported that application of ACPD onto hippocampal neurons leads to seizures and neuronal damage (Sacaan *et al.*, *Neurosci. Lett.* 139:77 (1992); Lipparti *et al.*, *Life Sci.* 52:85 (1993). Other studies indicate, however, that ACPD inhibits epileptiform activity, and also can exhibit neuroprotective properties. Taschenberger *et al.*, *Neuroreport* 3:629 (1992); Sheardown, *Neuroreport* 3:916 (1992); Koh *et al.*, *Proc. Natl. Acad. Sci. USA* 88:9431 (1991); Chiamulera *et al.*, *Eur. J. Pharmacol.* 216:335 (1992); Siliprandi *et al.*, *Eur. J. Pharmacol.* 219:173 (1992); Pizzi *et al.*, *J. Neurochem.* 61:683 (1993).

It is likely that these conflicting results are due to the lack of selectivity of ACPD, which causes activation of several different mGluR subtypes. In the studies finding neuronal damage it appears that Group I mGluRs were activated, thereby enhancing undesirable excitatory neurotransmission. In the studies showing neuroprotective effects it appears that activation of Group II and/or Group III mGluRs occurred, inhibiting presynaptic glutamate release, and diminishing excitatory neurotransmission.

This interpretation is consistent with the observation that (S)-4C3HPG, a Group I mGluR antagonist and Group II mGluR agonist, protects against audiogenic seizures in DBA/2 mice, while the Group II mGluR selective agonists DCG-IV and L-CCG-I protect neurons from NMDA- and KA-induced toxicity. Thomsen *et al.*, *J. Neurochem.* 62:2492 (1994); Bruno *et al.*, *Eur. J. Pharmacol.* 256:109 (1994); Pizzi *et al.*, *J. Neurochem.* 61:683 (1993).

Based on the foregoing, it is clear that currently available mGluR agonists and antagonists have limited value, due to their lack of potency and selectivity. In addition, most currently available compounds are amino acids or amino acid derivatives that have limited bioavailabilities, thereby hampering *in vivo* studies to assess mGluR physiology, pharmacology and their therapeutic potential. Compounds that selectively inhibit activation of metabotropic glutamate receptor Group I subtypes should be useful for treatment of neurological disorders and diseases such as senile dementia, Parkinson's disease, Alzheimer's disease, Huntington's Chorea, pain, epilepsy, head trauma, anoxic and ischemic injuries, and psychiatric disorders such as schizophrenia and depression.

- 6 -

It is apparent, therefore, that identification of potent mGluR agonists and antagonists with high selectivity for individual mGluR subtypes, particularly for Group I receptor subtypes, are greatly to be desired.

5

SUMMARY OF THE INVENTION

It is an object of the present invention, therefore, to identify metabotropic glutamate receptor-active compounds which exhibit a high degree of potency and selectivity for individual metabotropic glutamate receptor subtypes, and to provide methods of making these compounds.

10 It is a further object of this invention to provide pharmaceutical compositions containing compounds which exhibit a high degree of potency and selectivity for individual metabotropic glutamate receptor subtypes, and to provide methods of making these pharmaceutical compositions.

It is yet another object of this invention to provide methods of inhibiting activation of an mGluR Group I receptor, and of inhibiting neuronal damage caused by excitatory activation of an mGluR Group I receptor.

15 It is still another object of the invention to provide methods of treating a disease associated with glutamate-induced neuronal damage.

To accomplish these and other objectives, the present invention provides potent antagonists of Group I metabotropic glutamate receptors. These antagonists may be represented by the formula I.



wherein R is an optionally substituted straight or branched chain alkyl, arylalkyl, cycloalkyl, or alkylcycloalkyl group containing 5-12 carbon atoms. Ar is an optionally substituted aromatic, heteroaromatic, arylalkyl, or heteroaralkyl moiety containing up to 10 carbon atoms and up to 4 heteroatoms, and [linker] is $-(\text{CH}_2)_n-$, where n is 2-6, and wherein up to 4 CH_2 groups may independently be substituted with groups selected from the group consisting of $\text{C}_1\text{-C}_3$ alkyl, CHOH , CO , O , S , SO , SO_2 , N , NH , and NO . Two heteroatoms in the [linker] may not be adjacent except when those atoms are both N or are both NH. Two adjacent CH_2 groups in [linker] also may be replaced by a substituted or unsubstituted alkene or alkyne group. Pharmaceutically acceptable salts of the compounds also are provided.

- 7 -

In one embodiment of the invention, Ar comprises a ring system selected from the group consisting of benzene, thiazole, furyl, pyranyl, 2H-pyrrolyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, benzothiazole, benzimidazole, 3H-indolyl, indolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalizinyl, naphthyridinyl, quinazolinyl, cinnolinyl, isothiazolyl, quinoxalinyl, indolizinyl, isoindolyl, benzothienyl, benzofuranyl, isobenzofuranyl, and chromenyl rings. Ar optionally may independently be substituted with up to two C₁-C₃ alkyl groups, or up to two halogen atoms, where halogen is selected from F, Cl, Br, and I.

10 In another embodiment of the invention, R contains 4, 5, 6, 7, 8, 9, 10 or 11 carbon atoms, where some or all of the hydrogen atoms on two carbon atoms optionally may be replaced with substituents independently selected from the group consisting of F, Cl, OH, OMe, =O, and -COOH.

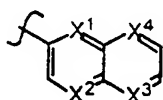
15 In yet another embodiment [linker] comprises an amide, ester, or thioester group.

In a preferred embodiment, R comprises a moiety selected from the group consisting of substituted or unsubstituted adamantyl, 2-adamantyl, (1S,2S,3S,5R)-isopinocampheyl, tricyclo[4.3.1.1(3,8)]undec-3-yl, (1S,2R,5S)-*cis*-myrtanyl, (1R,2R,4S)-isobornyl, (1R,2R,3R,5S)-isopinocampheyl, (1S,2S,5S)-*trans*-myrtanyl, (1R,2R,5R)-*trans*-myrtanyl, (1R,2S,4S)-bornyl, 1-adamantanemethyl, 3-noradamantyl, (1S,2S,3S,5R)-3-pinanemethyl, cyclooctyl, α,α -dimethylphenethyl, (S)-2-phenyl-1-propyl, cycloheptyl, 4-methyl-2-hexyl groups, 2,2,3,3,4,4,4-heptafluorobutyl, 4-ketoadamantyl, 3-phenyl-2-methylpropyl, 3,5-dimethyladamantyl, *trans*-2-phenylcyclopropyl, 2-methylcyclohexyl, 3,3,5-trimethylcyclohexyl, 2-(*o*-methoxyphenyl)ethyl, 2-(1,2,3,4-tetrahydronaphthyl), 4-phenylbutyl, 2-methyl-2-phenylbutyl, 2-(*m*-fluorophenyl)ethyl, 2-(*p*-fluorophenyl)ethyl, 2-(3-hydroxy-3-phenyl)propyl, (S)-2-hydroxy-2-phenylethyl, (R)-2-hydroxy-2-phenylethyl, 2-(3-*m*-chlorophenyl-2-methyl)propyl, 2-(3-*p*-chlorophenyl-2-methyl)propyl, 4-*tert*-butyl-cyclohexyl, (S)-1-(cyclohexyl)ethyl, 2-(3-(3,4-dimethylphenyl)-2-methyl)propyl, 3,3-dimethylbutyl, 2-(5-methyl)hexyl, 1-myrtanyl, 2-bornyl, 3-pinanemethyl, 2,2,3,3,4,4,5,5-octafluoropentyl, *p*-fluoro- α,α -dimethylphenethyl, 2-naphthyl, 2-bornanyl, cyclohexylmethyl, 3-methylcyclohexyl, 4-methylcyclohexyl, 3,4-dimethylcyclohexyl, 5-chloro-tricyclo[2.2.1]heptyl, *o*- α,α -dimethylphenethyl, 2-

- 3 -

indanyl, 2-spiro[4.5]decyl, 2-phenylethyl, 1-adamantylethyl, 1-(1-bicyclo[2.2.1]hept-2-yl)ethyl, 2-(2-methyl-2-phenylpropyl), 2-(*o*-fluorophenyl)ethyl, 1-(cyclohexyl)ethyl, and cyclohexyl.

In a still further embodiment of the invention, Ar comprises a group
 5 having the formula



where X¹, X², X³, and X⁴ independently can be N or CH, provided that
 10 not more than two of X¹, X², X³, and X⁴ can be N. In a preferred embodiment, X¹ is N, and/or X² is N. In another embodiment, X³ is N. In still another embodiment, X¹ is CH and X² is N.

In yet another embodiment, Ar is an optionally substituted 2-, 3-, or 4-pyridyl moiety, or Ar is a 6-benzothiazolyl moiety. The compound is selected
 15 from the group consisting of *N*-[6-(2-Methylquinolyl)]-1-adamantanecarboxamide, *N*-(6-Quinolyl)-1-adamantanecarboxamide, *N*-(2-Quinolyl)-1-adamantanecarboxamide, *N*-(3-Quinolyl)-1-adamantane-carboxamide, 6-Quinolyl-1-adamantanecarboxylate, 1-Adamantyl-6-quinolinecarboxylate, 2,2,3,3,4,4,5,5-Octafluoro-1-pentyl-6-quinolinecarboxylate, 1-
 20 Adamantanemethyl-6-quinolinecarboxylate, 1-Adamantyl-2-quinoxalinecarboxylate, *N*-(1-Adamantyl)-3-quinoline-carboxamide, *N*-(1-Adamantyl)-2-quinolinecarboxamide, *N*-(2-Adamantyl)-2-quinoxalinecarboxamide, *N*-[(1R,2R,3R,5S)-3-Pinanemethyl]-2-quinoxalinecarboxamide, *N*-(1-Adamantyl)-2-quinoxalinecarboxamide, *N*-(1-Adamantyl)-6-
 25 quinolinecarboxamide, *N*-(*exo*-2-Norbornanyl)-2-quinoxalinecarboxamide, *N*-[(1R,2S,4S)-Bornyl]-2-quinoxalinecarboxamide, *N*-(3-Noradamantyl)-2-quinoxalinecarboxamide, *N*-[(1R,2R,3R,5S)Iso-pinocamphenyl]-2-quinoxalinecarboxamide, *N*-[(1S,2S,3S,5R)-Isopinocamphenyl]-2-quinoxalinecarboxamide, *N*-(5-Chloro-[2.2.1.0]tricyclo-2.6-hepta-3-yl)-2-
 30 quinoxalinecarboxamide, *N*-([4.3.1.1]Tricyclo-3.8-undeca-3-yl)-2-quinoxalinecarboxamide, *N*-[(1S,2R,5S)-*cis*-Myrtanyl]-2-quinoxalinecarboxamide, *N*-[(1R,2R,4S)Isobornyl]-2-quinoxalinecarboxamide.

- 3 -

N-[endo-(±)-2-Norbornanyl]-2-quinoxalinecarboxamide, *N*-[(*R*)-2-Phenyl-1-propyl]-2-quinoxalinecarboxamide, *N*-[(*S*)-2-Phenyl-1-propyl]-2-quinoxalinecarboxamide, *N*-(2-Indanyl)-2-quinoxalinecarboxamide, 1-Adamantanemethyl 6-quinolyl ether, 1-Adamantyl-3-quinolinecarboxylate, *N*-(α,α-Dimethylphenethyl)-2-quinoxalinecarboxamide, *N*-(α,α-Dimethyl-2-chlorophenethyl)-2-quinoxalinecarboxamide, *N*-(α,α-Dimethyl-4-fluorophenethyl)-2-quinoxalinecarboxamide, *N*-(β-Methylphenethyl)-2-quinoxalinecarboxamide, *N*-(3-Methylcyclohexyl)-2-quinoxalinecarboxamide, *N*-(2,3-Dimethylcyclohexyl)-2-quinoxalinecarboxamide, *N*-[(1*S*,2*S*,3*S*,*S**R*)-3-Pinanemethyl]-2-quinoxaline-carboxamide, *N*-(1-Adamantanemethyl)-2-quinoxaline-carboxamide, *N*-(4-Methylcyclohexyl)-2-quinoxaline-carboxamide, *N*-[(1*S*,2*S*,5*S*)-*trans*-Myrtanyl]-2-quinoxaline-carboxamide, and *N*-[(1*R*,2*R*,5*R*)-*trans*-Myrtanyl]-2-quinoxalinecarboxamide, and pharmaceutically acceptable salts thereof.

In a preferred embodiment, the compound is selected from the group consisting of *N*-(1-Adamantyl)-3-quinolinecarboxamide, *N*-(1-Adamantyl)-2-quinolinecarboxamide, *N*-(2-Adamantyl)-2-quinoxaline-carboxamide, *N*-[(1*R*,2*R*,3*R*,5*S*)-3-Pinanemethyl]-2-quinoxaline-carboxamide, *N*-(1-Adamantyl)-2-quinoxaline-carboxamide, *N*-(1-Adamantyl)-6-quinolinecarboxamide, *N*-(exo-2-Norbornanyl)-2-quinoxaline-carboxamide, *N*-[(1*R*,2*S*,4*S*)-Bornyl]-2-quinoxaline-carboxamide, *N*-(3-Noradamantyl)-2-quinoxaline-carboxamide, *N*-[(1*R*,2*R*,3*R*,5*S*)-Isopinocampheyl]-2-quinoxaline-carboxamide, *N*-[(1*S*,2*S*,3*S*,5*R*)-Isopinocampheyl]-2-quinoxaline-carboxamide, *N*-(5-Chloro-[2.2.1.0]tricyclo-2,6-hepta-3-yl)-2-quinoxaline-carboxamide, *N*-([4.3.1.1]Tricyclo-3,8-undeca-3-yl)-2-quinoxaline-carboxamide, *N*-[(1*S*,2*R*,5*S*)-*cis*-Myrtanyl]-2-quinoxaline-carboxamide, *N*-[(1*R*,2*R*,4*S*)Isobornyl]-2-quinoxaline-carboxamide, *N*-[endo-(±)-2-Norbornanyl]-2-quinoxaline-carboxamide, *N*-[(1*S*,2*S*,3*S*,5*R*)-3-Pinanemethyl]-2-quinoxalinecarboxamide, *N*-(1-Adamantanemethyl)-2-quinoxalinecarboxamide, *N*-[(1*S*,2*S*,5*S*)-*trans*-Myrtanyl]-2-quinoxalinecarboxamide, and *N*-[(1*R*,2*R*,5*R*)-*trans*-Myrtanyl]-2-quinoxalinecarboxamide, and pharmaceutically acceptable salts thereof.

In another embodiment, the compound is selected from the group consisting of *N*-[6-(2-Methylquinolyl)]-1-adamantanecarboxamide, *N*-(6-Quinolyl)-1-adamantane-carboxamide, *N*-(2-Quinolyl)-1-adamantanecarboxamide.

and *N*-(3-Quinolyl)-1-adamantanecarboxamide, *N*-(3-Methylcyclohexyl)-2-quinoxalinecarboxamide, *N*-(2,3-Dimethylcyclohexyl)-2-quinoxalinecarboxamide, *N*-[(1*S*,2*S*,3*S*,5*R*)-3-Pinanemethyl]-2-quinoxalinecarboxamide, *N*-(1-Adamantanemethyl)-2-quinoxalinecarboxamide, and *N*-(4-Methylcyclohexyl)-2-quinoxalinecarboxamide, *N*-[(*R*)-2-Phenyl-1-propyl]-2-quinoxalinecarboxamide, *N*-[(*S*)-2-Phenyl-1-propyl]-2-quinoxalinecarboxamide, *N*-(2-Indanyl)-2-quinoxalinecarboxamide, *N*-(α - α -Dimethylphenethyl)-2-quinoxalinecarboxamide, *N*-(α , α -Dimethyl-2-chlorophenethyl)-2-quinoxalinecarboxamide, *N*-(α , α -Dimethyl-4-fluorophenethyl)-2-quinoxalinecarboxamide, and *N*-(β -Methylphenethyl)-2-quinoxalinecarboxamide, 1-Adamantanemethyl 6-quinolyl ether, 6-Quinolyl-1-adamantanecarboxylate, 1-Adamantyl-6-quinolinecarboxylate, 2,2,3,3,4,4,5,5-Octafluoro-1-pentyl 6-quinolinecarboxylate, 1-Adamantanemethyl 6-quinolinecarboxylate, 1-Adamantyl-2-quinoxalinecarboxylate, and 1-Adamantyl-3-quinolinecarboxylate, and pharmaceutically acceptable salts thereof.

In yet another embodiment, the compound is selected from the group consisting of 3-(1-Adamantanemethoxy)-2-chloroquinoxaline, 2-(1-Adamantanemethoxy)-3-methylquinoxaline, 3-(1-Adamantanemethoxy)-2-fluoroquinoxaline, 2-(1-Adamantanemethoxy)-3-trifluoromethylquinoxaline, *N*-[2-(4-Phenylthiazolyl)]-1-adamantanecarboxamide, *N*-[2-(5-Methyl-4-phenylthiazolyl)]-1-adamantanecarboxamide, 1-(1-Adamantyl)-2-(benzothiazol-2-ylsulfanyl)ethanone, *N*-(1-Adamantyl)-2-chloroquinoxaline-3-carboxamide, *N*-(1-Adamantyl)-3-methylquinoxaline-2-carboxamide, and *N*-(1-Adamantyl)-1-oxyquinoxaline-3-carboxamide, 4-Chlorophenyl 3-coumarincarboxylate, 2-(1-Adamantanemethylsulfanyl)quinoxaline, 3-(1-Adamantanemethoxy)-2-chloropyrazine, 1-(1-Adamantyl)-2-(4,6-dimethylpyrimidin-2-ylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(2-anisylsulfanyl)ethanone, 3-(1-Adamantanemethoxy)-1*H*-quinoxalin-2-one, 1-(1-Adamantyl)-2-(3-anisylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(4-anisylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(4-chlorophenylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(2-naphthylsulfanyl)ethanone, *N*-(2-[6-(1-Piperidinyl)pyrazinyl])-1-adamantanecarboxamide, *N*-(2-[6-(1-Piperidinyl)pyrazinyl])adamantan-1-ylmethylcarboxamide, 1-(1-Adamantyl)-2-(1-naphthylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(8-quinolylsulfanyl)ethanone hydrochloride, 1-(1-Adamantyl)-2-(4-

- 11 -

trifluoromethoxyphenoxy)ethanone, 2-(1-Adamantanemethoxy)quinoxaline, *N*-(*trans*-4-Methylcyclohexyl)-2-quinoxalinecarboxamide, *N*-(*cis*-4-Methylcyclohexyl)-2-quinoxalinecarboxamide, *N*-(*trans*-4-Methylcyclohexyl)-2-quinolinecarboxamide, *N*-(*trans*-4-Methylcyclohexyl)-3-quinolinecarboxamide, and *N*-(*trans*-4-Methylcyclohexyl)-6-quinolinecarboxamide, 2-(1-Adamantanemethylsulfinyl)-benzothiazole, *N*-(4-Phenylbutyl)-2-quinoxalinecarboxamide, 1-(1-Adamantyl)-2-(4, 6-dimethylpyrimidin-2-ylsulfonyl)ethanol, 1-(1-Adamantyl)-2-(3-chloroquinoxal-2-yl)ethanone, 2-(1-Adamantanemethylsulfonyl)-3-methylquinoxaline, *N*-(1-Adamantyl)-2-anisamide, *N*-(1-Adamantanemethyl)-2-anisamide, 1-(1-Adamantyl)-2-(4-chlorophenylsulfonyl)ethanone, 2-(1-Adamantanemethylsulfonyl)-3-methylquinoxaline, 1-(1-Adamantyl)-2-(4-fluorophenylsulfonyl)ethanone, 1-(1-Adamantyl)-2-(3-fluorophenylsulfonyl)ethanone, 1-(1-Adamantyl)-2-(2-methoxyphenoxy)ethanone, 1-(4-Anisylsulfonyl)butan-2-one, 1-(1-Adamantyl)-2-(4-anisidiny)ethanone hydrochloride, 3, 3-Dimethyl-1-(4-anisylsulfonyl)butan-2-one, 1-(4-Biphenyl)-2-(4-anisylsulfonyl)ethanone, 1-(1-Adamantyl)-2-(2-trifluoromethoxyphenylsulfonyl)ethanone, 1-(1-Adamantyl)-2-(3-methylquinoxal-2-ylsulfonyl)ethanone, 1-(1-Adamantyl)-2-(2-anisidiny)ethanone hydrochloride, 1-(1-Adamantyl)-2-(4-trifluoromethoxyphenylamino)ethanone hydrochloride, 1-(1-Adamantyl)-2-(*N*-methyl-4-anisidiny)ethanone hydrochloride, *N*-(1-Adamantyl)-7-trifluoromethylquinoline-3-carboxamide, *N*-(1-Adamantyl)-2-(1-piperiziny)quinoxaline-3-carboxamide, *N*-(1-Adamantyl)-2-(2-aminoethylamino)quinoxaline-3-carboxamide, Methyl *N*-(3-quinolyl)-3-carboxyadamantane-1-carboxamide, 1-(1-Adamantyl)-2-[(*R*)-1-(1-naphthyl)ethan-1-ylamino]ethanone, *N*-(1-Adamantyl)-2-methoxyquinoxaline-3-carboxamide, Ethyl *N*-(1-adamantyl)-2-(3-propanoylamino)quinoxaline-3-carboxamide, *N*-(4-Chlorophenyl)-2, 3-dimethylquinoxaline-6-carboxamide, *N*-(1-Adamantyl)-6, 7-dimethylquinoxaline-2-carboxamide, *N*-((*S*)-1-Tetralinyl)-2-quinoxalinecarboxamide, *N*-(4-Chlorophenethyl)-2-quinoxalinecarboxamide, *N*-(6-Quinolyl)-2-quinoxalinecarboxamide, *N*-(1-Tetralinmethyl)-2-quinoxalinecarboxamide, *N*-(1-Indanmethyl)-2-quinoxalinecarboxamide, *N*-(4, 4-Dimethylcyclohexyl)-2-quinoxalinecarboxamide, and pharmaceutically acceptable salts thereof.

- 12 -

In accordance with another embodiment of the invention, there has been provided a pharmaceutical composition comprising a compound as set forth above, together with a pharmaceutically acceptable diluent or excipient.

5 In accordance with still another embodiment of the invention, there has been provided a method of making a compound as set forth above, comprising reacting a compound containing an activated carboxylic acid group with a compound containing an amine, hydroxyl, or thiol group.

10 In accordance with a still further embodiment of the invention, there has been provided a method of inhibiting activation of an mGluR Group I receptor, comprising treating a cell containing said mGluR Group I receptor with an effective amount of a compound as set forth above.

15 In yet another embodiment of the invention, there has been provided a method of inhibiting neuronal damage caused by excitatory activation of an mGluR Group I receptor, comprising treating neurons with an effective amount of a compound as set forth above.

20 In accordance with a further embodiment of the invention, there has been provided a method of treating a disease associated with glutamate-induced neuronal damage, comprising administering to a patient suffering from said disease an effective amount of a composition as set forth above.

25 Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows illustrative compounds of the invention.

30

- 13 -

DETAILED DESCRIPTION

The invention provides compounds that are potent and selective antagonists of Group I metabotropic glutamate receptors. The compounds contemplated by the invention can be represented by the general formula I:

5



where R is a straight or branched chain alkyl, arylalkyl, or optionally substituted alicyclic group, and Ar is an optionally substituted aromatic, heteroaromatic, arylalkyl, or heteroaralkyl moiety. The [linker] moiety is a group that not only covalently binds to the Ar and R moieties, but also facilitates adoption of the correct spatial orientation by Ar and R to allow receptor binding.

Structure of the Ar moiety

The Ar moiety generally may contain up to ten carbon atoms, although the skilled artisan will recognize that Ar groups with more than ten carbon atoms are within the scope of the invention. Ar can be a monocyclic or fused bicyclic aryl, alkaryl, heteroaryl or heteroarylalkyl group. The ring systems encompassed by Ar can contain up to four heteroatoms, independently selected from the group consisting of N, S, and O. When Ar is a heteroaryl ring or ring system, it preferably contains one or two heteroatoms. At least one of the heteroatoms preferably is N.

Monocyclic Ar groups include, but are not limited to: phenyl, thiazoyl, furyl, pyranal, 2H-pyrrolyl, thienyl, pyrrolyl, imidazoyl, pyrazoyl, pyridyl, pyrazinyl, pyrimidinyl, and pyridazinyl moieties. Fused bicyclic Ar groups include, but are not limited to: benzothiazole, benzimidazole, 3H-indolyl, indolyl, indazoyl, purinyl, quinoliziny, isoquinolyl, quinolyl, phthaliziny, naphthyridinyl, quinazolinyl, cinnoliny, isothiazolyl, quinoxalinyl indoliziny, isoindolyl, benzothienyl, benzofuranyl, isobenzofuranyl, and chromenyl moieties. Ar preferably is a quinoxalinyl, quinoliny, or pyridyl moiety.

Other Ar moieties include the 3,4-methylenedioxy and 3,4-dioxane rings. The Ar moiety optionally may independently be substituted with up to two C₁-C₃

alkyl groups, or up to two halogen atoms, where halogen is selected from F, Cl, Br, and I.

Structure of the R moiety

5 The R moiety generally may contain between four and eleven carbon atoms, although the skilled artisan will recognize that R moieties with 12, 13, 14, 15, or 16 carbon atoms will be possible. Although R can contain 4, 5 or 6 carbon atoms, preferably R contains at least 7 carbon atoms. Preferably, R is optionally substituted alkyl, cycloalkyl, cycloalkylmethyl, or optionally substituted phenylalkyl. Generally, some or all of the hydrogen atoms on up to 10 two methine, methylene, or methyl groups of R may be replaced by substituents independently selected from the group consisting of F, Cl, OH, OMe, =O, and -COOH groups. However, more than two hydrogen atoms may be replaced with fluorine, and R may be perfluorinated.

15 Exemplary R moieties include, but are not limited to: adamantyl, 2-adamantyl, (1S,2S,3S,5R)-isopinocampheyl, tricyclo[4.3.1.1(3.8)]undec-3-yl, (1S,2R,5S)-*cis*-myrtanyl, (1R,2R,4S)-isobornyl, (1R,2R,3R,5S)-isopinocampheyl (1S,2S,5S)-*trans*-myrtanyl (1R,2R,5R)-*trans*-myrtanyl, (1R,2S,4S)-bornyl, 1-adamantanemethyl, 3-noradamantyl (1S,2S,3S,5R)-3-pinanemethyl, cyclooctyl, dimethylphenethyl, (S)-2-phenyl-1-propyl, cycloheptyl, 20 and 4-methyl-2-hexyl groups. Each of these exemplary R moieties may also be substituted in the manner set forth above.

Other preferred R groups include 2,2,3,3,4,4,4-heptafluorobutyl, 4-ketoadamantyl, 3-phenyl-2-methylpropyl, 3,5-dimethyladamantyl, *trans*-2-phenylcyclopropyl, 2-methylcyclohexyl, 3,3,5-trimethylcyclohexyl, 2-(*o*-methoxyphenyl)ethyl, 2-(1,2,3,4-tetrahydronaphthyl), 4-phenylbutyl, 2-methyl-2-phenylbutyl, 2-(*m*-fluorophenyl)ethyl, 2-(*p*-fluorophenyl)ethyl, 2-(3-hydroxy-3-phenyl)propyl, (S)-2-hydroxy-2-phenylethyl, (R)-2-hydroxy-2-phenylethyl, 2-(3-*m*-chlorophenyl-2-methyl)propyl, 2-(3-*p*-chlorophenyl-2-methyl)propyl, 4-*tert*-butyl-cyclohexyl, (S)-1-(cyclohexyl)ethyl, 2-(3-(3,4-dimethylphenyl)-2-methyl)propyl, 3,3-dimethylbutyl, 2-(5-methyl)hexyl, 1-myrtanyl, 2-bornyl, 3-pinanemethyl, 2,2,3,3,4,4,5,5-octafluoropentyl, *p*-fluoro-2,2-dimethylphenethyl, 2-naphthyl, 2-bornanyl, cyclohexylmethyl, 3-methylcyclohexyl, 4-methylcyclohexyl, 3,4-dimethylcyclohexyl, 5-chloro-

-15-

tricyclo[2.2.1]heptyl, *o*- , -dimethylphenethyl, 2-indanyl, 2-spiro[4.5]decyl, 2-phenylethyl, 1-adamantylethyl, 1-(1-bicyclo[2.2.1]hept-2-yl)ethyl, 2-(2-methyl-2-phenylpropyl), 2-(*o*-fluorophenyl)ethyl, 1-(cyclohexyl)ethyl, cyclohexyl, butan-2-onyl, diphenylene, 3-carboxyladamantyl, 1-tetrahydronaphthelenyl, 1-indanyl, 4-methylcyclohexyl, and 4,4-dimethylcyclohexyl moieties. Again, each of these
 5 exemplary R moieties may be substituted in the manner set forth above. When compounds may be present in alternative isomeric configurations, for example, *trans* or *cis*-4-methylcyclohexyl, the R moiety may have any of the possible configurations. Similarly, if a compound exists as enantiomers, the R moiety can
 10 be either of the enantiomers, or may be a racemate.

Structure of the [linker] moiety

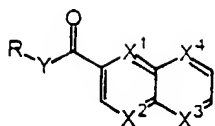
The [linker] moiety generally has the structure $-(CH_2)_n-$, where n is 2-6. Up to four CH_2 groups may independently be replaced with groups selected from
 15 the group consisting of a C_1 - C_3 alkyl group, CHOH, CO, O, S, SO, SO₂, N, NH, and NO, provided that two heteroatoms may not be adjacent except when those atoms are both N (forming an -N=N- linkage) or are both NH (forming an -NH-NH- linkage). Any two adjacent CH_2 groups also may be replaced by an alkene or alkyne group.

20 In a preferred embodiment, [linker] comprises an amide, ester, thioester, ketomethylene, ether, alkylether, ethylene, ethenyl, acetylenyl, hydroxyalkyl, alkylsulfone, or alkyl alkylsulfoxide group. Preferably, [linker] is an $-O-(CH_2)_m-$, $-CO-Y-(CH_2)_m-$, or $-S(O)_n-(CH_2)_m-$ group, where Y is CH_2 , NH, O, or S, and m is 1-4, and n is 0-2. The [linker] moiety may have either one of two possible
 25 orientations with respect to the R and Ar groups. Thus, for example, the invention encompasses compounds having the configuration $R-O-(CH_2)_m-Ar$ and $R-(CH_2)_m-O-R$.

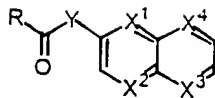
Design and synthesis of mGluR Group I antagonists

30 In one embodiment, compounds according to the invention are esters and amides of monocyclic or fused bicyclic aromatic and heteroaromatic carboxylic acids, phenols and amines. In a preferred embodiment, the compounds may be represented by the Formulae II or III:

- 16 -

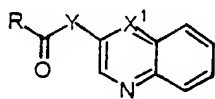


II

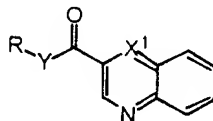


III

5 In Formulae II and III, Y can be either O, S, NH, or CH₂; and X¹, X², X³, and X⁴ independently can be N or CH. Preferably, one or two of X¹, X², X³, and X⁴ are N, and the remainder are CH. Preferred compounds contemplated by the invention have the formula IV or V, where R, Y and X¹ are as defined above.

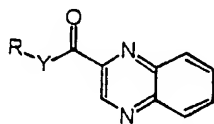


IV

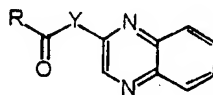


V

10 In another preferred embodiment of the invention, the compounds have the Formulae VI or VII :



VI

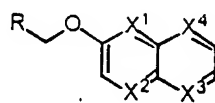


VII

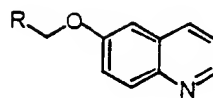
15 where R and Y are as defined above. In a first embodiment of the compounds of Formula VI, Y is N, R is an unsubstituted or monosubstituted 1,1-dimethylphenylethylamine or 1,1-dimethylbenzylamine moiety, where the
20 substituent preferably is an *o*-, *m*-, or *p*-chlorine or *p*-methoxy group. In a second embodiment of the compounds of Formula VI, Y is N, and R is an *o*-, *m*-, or *p*-methoxy substituted phenylethylamine. Compounds of the first and second
25 embodiments appear to exhibit selectivity for the mGluR₁ receptor. In a third embodiment, of the compounds of Formula VI, Y is N, and R is an *o*, *m*, or *p*-fluoro-substituted phenylethylamine. Compounds of the third embodiment appear not to discriminate between the mGluR₁ and mGluR₃ receptor subtypes.

- 17 -

In yet another preferred embodiment of the invention, the compounds have the Formulae VIII or IX:



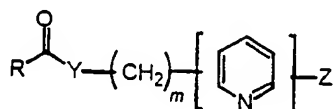
VIII



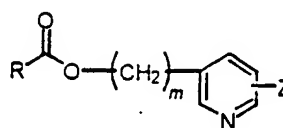
IX

wherein X^{1-4} and R are as defined above. In a first embodiment of compounds of Formula VIII, X^1 and X^2 are N, X^3 and X^4 are H. R is 1-adamantyl, and a substituent is present on the carbon atom ortho to both the linker and X^2 . The substituent preferably is a halogen, such as chlorine, or an alkyl group, such as methyl. In a second embodiment of compound IX, R is 1-adamantyl. Compounds of these first and second embodiments appear to exhibit selectivity for the mGluR₁ receptor.

In still another embodiment, the compounds may have the Formulae X or XI, where Z is a pharmaceutically acceptable substituent. The skilled artisan will recognize that pharmaceutically acceptable Z groups are those groups that do not deleteriously reduce the receptor binding activity of the compound. Suitable Z groups include, but are not limited to halogen, lower alkyl, oxygen or amine, and their pharmaceutically acceptable derivatives including ethers, esters, and amides. Preferably, Z contains 0-4 carbon atoms.



X



XI

In each of the compounds described above, "alkyl" denotes both straight and branched chain alkyl. In other embodiments, R is adamantyl, the linker is -CO-CH₂-S-, and Ar is *m*- or *o*-alkyloxyphenyl, or 3,4-methylenedioxy or 3,4-dioxane.

In general, it appears that selective antagonism of the mGluR₁ receptor can be attained with compounds of the formula R-CO-N-Ar₁, where Ar₁ is an

- 18 -

aromatic or heteroaromatic group such as a quinoliny, quinoxaliny, thiazolidiny, phenyl, benzimidazoyl, or pyridyl group.

The skilled artisan also will recognize that the compounds of the invention encompass salts of the compounds described above. These salts include
5 pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts or optionally alkylated ammonium salts, such as hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, trifluoroacetic, malonic, succinic, citric, mandelic, benzoic, cinnamic, methanesulfonic and similar ones, and include acids
10 related to the pharmaceutically acceptable salts listed in the *Journal of Pharmaceutical Sciences*, 66:2 (1977) and incorporated herein by reference.

Examples of compounds according to the present invention are set forth in Table 1 below.

Preparation of mGluR Group I antagonists

15 The skilled artisan will recognize that mGluR Group I antagonists according to the invention may be prepared by methods that are well known in the art, using widely recognized techniques of organic chemistry. Suitable reactions are described in standard textbooks of organic chemistry. For example, see March, Advanced Organic Chemistry, 2d ed., McGraw Hill (1977).

20 For example, the compounds generally may be prepared by formation of the [linker] moiety between two precursor compounds containing suitable Ar and R moieties. When the linker contains an amide linkage, the amide may be formed using well known techniques, such as reaction between an amine and an acid chloride, or by reaction in the presence of a coupling reagent such as
25 carbonyldiimidazole, or a carbodiimide such as, for example, 1,3-dicyclohexylcarbodiimide (DCC). Formation of ester and thioester linkages can be achieved in similar fashion.

When the [linker] moiety contains an ether linkage, the ether function also can be prepared using standard techniques. For example, ethers can be formed
30 using the Mitsunobu reaction, where a primary alcohol function is displaced by another hydroxy group via activation using PPh₃ and diethylazodicarboxylate (DEAD). Thioether linkages may be prepared by displacement of a leaving group such as halide with a thiolate anion, generated by deprotonation of a thiol group with base.

When the [linker] moiety contains a ketomethylene group, it can be formed by alkylation of a ketone enolate. Thus, for example, a methyl ketone can be deprotonated using a strong base such as lithium diisopropylamide (LDA), followed by reaction with an alkyl halide. Alternatively, a ketomethylene
5 function can be prepared via addition of an organometallic compound, such as a Grignard reagent, to an aldehyde, followed by oxidation of the resultant hydroxyl group to a ketone. Suitable reagents for oxidizing alcohols to ketones are well known in the art.

[Linker] moieties containing other heteroatom groups also may be
10 prepared using methods that are well known in the art. *N,N'*-Disubstituted hydrazine compounds may be prepared via reductive amination of hydrazones formed by reaction of a monosubstituted hydrazone with an aldehyde. *N,N'*-Disubstituted azo compounds can be formed, for example, by oxidation of the corresponding hydrazines.

15 In most cases, the precursor Ar and R moieties are readily available, or may be prepared using straightforward techniques of organic chemistry. Many compounds are commercially available, for example, from Aldrich Chemical Company, Milwaukee, WI. When the compounds are not commercially available, they may readily prepared from available precursors using
20 straightforward transformations that are well known in the art.

For example, carboxylic acids may be converted into the corresponding acid chlorides by reaction with, for example, thionyl chloride or oxalyl chloride. An example of such a reaction is provided below in Example 3. Compounds containing a hydroxy function may be converted into the corresponding amine by
25 (i) conversion of the hydroxyl group into a leaving group, such as a sulfonic acid ester (such as a triflate, mesylate, or tosylate) or a halide, (ii) displacement with azide ion, and (iii) reduction of the resulting azide by, for example, hydrogenation over a platinum oxide catalyst. An illustration of such a transformation is provided below in Example 12.

30

Testing of compounds for mGluR Group I antagonist activity

The pharmacological properties of the compounds of the invention can be analyzed using standard assays for functional activity. Examples of glutamate receptor assays are well known in the art, for example, see Aramori *et al.*,

- 20 -

Neuron 8:757 (1992); Tanabe *et al.*, *Neuron* 8:169 (1992). The methodology described in those publications is incorporated herein by reference.

Conveniently, the compounds of the invention may be studied using an assay that measures inhibition of intracellular calcium mobilization in cells
5 expressing recombinant receptors that can bind the compounds. Suitable receptor constructs are well known in the art and are also described, for example, in WO 97/05252, the contents of which are hereby incorporated by reference in their entirety.

Thus, HEK-293 cells (human embryonic kidney cells, available from the
10 American Type Culture Collection, Rockville, MD, Accession Number CRL 1573) are stably transfected with a DNA construct expressing a recombinant receptor. The stably transfected cells are cultured in high glucose DMEM (Gibco 092) containing 0.8 mM glutamine, 10% FBS, and 200 μ M hygromycin B.

A protocol for measuring intracellular calcium mobilization in response to
15 changes in extracellular calcium using the calcium-sensitive dye Fura has been described previously. Briefly, HEK-293 cells, stably transfected with a DNA construct encoding a recombinant receptor, are loaded with Fura dye. The cells then are washed, resuspended, and maintained at 37 °C. The cells are diluted into cuvettes for recording fluorescent signals. Measurements of fluorescence are
20 performed at 37 °C using standard methods, and concentrations of intracellular Ca^{2+} are calculated using a dissociation constant (K_d) of 224 nM and applying equation:

$$[\text{Ca}^{2+}]_i = (F - F_{\min} / F_{\max}) \times K_d$$

25

where F is fluorescence at any particular time of interest, F_{\min} is determined by chelating all calcium available, therefore, no fura 2 is bound to calcium, and F_{\max} is determined by fully saturating all the fura 2 available with calcium.

A detailed protocol for testing the compounds of the invention is provided
30 below at Example 15.

- 21 -

Preparation of pharmaceutical compositions containing mGluR antagonists, and their use in treating neurological disorders

The compounds of the invention are useful for treating neurological disorders or diseases. While these compounds will typically be used in therapy for human patients, they may also be used in veterinary medicine to treat similar or identical diseases.

In therapeutic and/or diagnostic applications, the compounds of the invention can be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in Remington's Pharmaceutical Sciences: Drug Receptors and Receptor Theory, 18th ed., Mack Publishing Co. (1990).

The compounds according to the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.01 to about 1000 mg, preferably from about 0.5 to about 100 mg, per day may be used. A most preferable dosage is about 2 mg to about 70 mg per day. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

Pharmaceutically acceptable salts are generally well known to those of ordinary skill in the art, and may include, by way of example but not limitation, acetate, benzenesulfonate, besylate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/disphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, or teoclate. Other pharmaceutically acceptable salts may be found in, for example, Remington's Pharmaceutical Sciences: (18th ed.), Mack Publishing Co., Easton, PA (1990).

Preferred pharmaceutically acceptable salts include, for example, acetate, benzoate, bromide, carbonate, citrate, gluconate, hydrobromide, hydrochloride,

- 22 -

maleate, mesylate, napsylate, pamoate (embonate), phosphate, salicylate, succinate, sulfate, or tartrate.

Depending on the specific conditions being treated, such agents may be formulated into liquid or solid dosage forms and administered systemically or locally. The agents may be delivered, for example, in a timed- or sustained-release form as is known to those skilled in the art. Techniques for formulation and administration may be found in Remington's Pharmaceutical Sciences: (18th ed.), Mack Publishing Co., Easton, PA (1990). Suitable routes may include oral, buccal, sublingual, rectal, transdermal, vaginal, transmucosal, nasal or intestinal administration: parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections, just to name a few.

For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

Use of pharmaceutically acceptable carriers to formulate the compounds herein disclosed for the practice of the invention into dosages suitable for systemic administration is within the scope of the invention. With proper choice of carrier and suitable manufacturing practice, the compositions of the present invention, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

- 23 -

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. The preparations formulated
5 for oral administration may be in the form of tablets, dragees, capsules, or solutions.

Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if
10 desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethyl-cellulose (CMC), and/or polyvinylpyrrolidone (PVP:
15 povidone). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum
20 arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-stuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

25 Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally,
30 stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGs). In addition, stabilizers may be added.

- 24 -

The present invention, thus generally described, will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

5

EXAMPLES

General Experimental Methods

Capillary gas chromatographic and mass spectral data were obtained using a Hewlett-Packard (HP) 5890 Series II Gas Chromatograph coupled to an HP
10 5971 Series Mass Selective Detector [Ultra-2 Ultra Performance Capillary Column (crosslinked 5% PhMe silicone); column length, 25 m; column i.d., 0.20 mm; helium flow rate, 60 mL/min; injector temp., 250 °C; temperature program, 20 C/min from 125 to 325 °C for 10 min. then held constant at 325 °C for 6 min]. Thin-layer chromatography was performed using Analtech Uniplat
15 250-µm silica gel HF TLC plates. UV light sometimes in conjunction with ninhydrin and Dragendorff's spray reagents (Sigma Chemical Co.) were used for detecting compounds on the TLC plates. Reagents used in reactions were purchased from the Aldrich Chemical Co. (Milwaukee, WI), Sigma Chemical Co. (Saint Louis, MO), Fluka Chemical Corp. (Milwaukee, WI), Fisher
20 Scientific (Pittsburgh, PA), TCI America (Portland, OR), or Lancaster Synthesis (Windham, NH).

EXAMPLE 1: Preparation of *N*-[6-(2-Methylquinolyl)]-1-adamantanecarboxamide (40)
25

2-Methyl-6-aminoquinoline

A mixture of 2-methyl-6-nitroquinoline (1.00 g, 5.31 mmol) and Pearlman's catalyst [palladium dihydroxide on activated charcoal (~20% palladium); 0.10 g] in ethyl acetate (40 mL) was stirred under hydrogen gas
30 (1 atm) at 60°C for 1.5 h. The reaction mixture was filtered and the filtrate was rotary evaporated. This provided 0.81 g (96%) of 2-methyl-6-aminoquinoline as a yellow solid.

- 25 -

N-[6-(2-Methylquinolyl)]-1-adamantanecarboxamide (40)

1-Adamantanecarbonyl chloride (1.02 g, 5.13 mmol) in pyridine (2 mL) was added to a solution of 2-methyl-6-aminoquinoline (0.81 g, 5.1 mmol) in pyridine (8 mL). The reaction was stirred for 17 h. To the stirring reaction mixture was added water (100 mL) which caused the product to precipitate.. This precipitate was filtered and then washed with water (3 x 25 mL) and diethyl ether (3 x 25 mL). This provided 1.07 g (65%) of (40) as a cream-colored powder:

rt=13.49 min.: m/z (rel. int.) 320 (M+,30), 235 (8), 158 (4), 157 (6), 136 (11), 135 (100), 130 (11), 107 (7), 93 (15), 91 (8), 79 (18), 77 (11), 67 (6).

In a similar manner, the following *N*-quinolyl-1-adamantanecarboxamides were prepared:

N-(6-Quinolyl)-1-adamantanecarboxamide (18)

Prepared from 1-adamantanecarbonyl chloride (1.37 g, 6.90 mmol), 6-aminoquinoline (0.59 g, 4.1 mmol), pyridine (20 mL), and water (200 mL) yielding 1.25 g (100%) of (18):

rt=13.24 min.:m/z (rel. int.) 306 (M+,23), 221 (6), 144 (3), 136 (12), 135 (100), 116 (10), 107 (7), 93 (15), 91 (8), 79 (18), 77 (9), 67 (7), 41 (6).

N-(2-Quinolyl)-1-adamantanecarboxamide hydrochloride (81)

Prepared from 1-adamantanecarbonyl chloride (0.75 g, 3.8 mmol), 2-aminoquinoline (0.60 g, 4.2 mmol), pyridine (10 mL), and water (100 mL).

Forming the hydrochloride salt with diethyl ethereal hydrogen chloride yielded 0.19 g (15%) of (81):

rt=12.24 min;m/z (rel. int.) 306 (M+,80), 305 (23), 277 (8), 263 (8), 221 (10), 172 (9), 171 (72), 145 (16), 144 (61), 143 (13), 136 (11), 135 (100), 128 (33), 117 (17), 116 (24), 107 (18), 105 (8), 101 (10), 93 (40), 91 (29), 89 (13), 81 (14), 79 (55), 77 (35), 67 (18), 65 (10), 55 (12), 53 (10), 41 (20).

N-(3-Quinolyl)-1-adamantanecarboxamide (86)

Prepared from 1-adamantanecarbonyl chloride (0.75 g, 3.8 mmol), 3-aminoquinoline (0.60 g, 4.2 mmol), pyridine (10 mL), and water (100 mL) yielding 0.33 g (29%) of (86):

rt=13.01 min.: m/z (rel. int.) 306 (M+,22), 136 (11), 135 (100), 116 (11), 107 (8), 93 (15), 91 (8), 89 (7), 79 (17), 77 (8), 67 (6), 65 (3).

N-(*trans*-4-Methylcyclohexyl)-2-quinoxalinecarboxamide (299)

Using the method of Booth (J. Chem. Soc., 1958, 2688; J. Chem. Soc., 1971, 1047; Tetrahedron, 1967, 23, 2421), hydroxylamine (3.8 g, 55 mmol),
5 ethanol (50 mL), pyridine (4.44 mL, 55 mmol), and 4-methyl cyclohexanone (6.1 mL, 50 mmol) were stirred at ambient temperature for 16 hours and then heated at reflux for 15 minutes. The ethanol was then removed in vacuo and the residual oil dissolved in ethylacetate (100 mL). The organic layer was washed with water (2X), brine, dried over anhydrous MgSO₄, filtered, and concentrated
10 to a clear oil (the oxime product), which crystallized upon standing.

Without further purification 1.9 g (15 mmol) of the intermediate oxime in absolute ethanol (40 mL) was heated to reflux and treated with (in small portions) sodium metal (4 g). The reaction was heated at reflux until the sodium was consumed. The reaction was cooled and treated with water (10 mL). The
15 reaction was transferred into a flask containing ice and concentrated HCl (6 mL). The ethanol was removed in vacuo and the remaining aqueous phase washed with diethyl ether (3X, to remove unreduced oxime). The remaining aqueous phase was concentrated to afford 1.8 g of a white crystalline solid (the *trans*-4-methylcyclohexylamine hydrochloride product).

20 Without further purification 750 mg (5 mmol) of *trans*-4-methylcyclohexyl amine hydrochloride in dichloromethane (10 mL) was treated with pyridine (1.62 mL, 20 mmol) followed by the addition of 2-quinoxaloyl chloride (963 mg, 55 mmol). The reaction was stirred at ambient temperature for 16 hours and diluted with chloroform (25 mL). The organics were washed
25 with 10% HCl (3X), 1 N NaOH (3X), brine, dried over anhydrous MgSO₄, filtered and concentrated to a solid. Chromatography (MPLC) of the crude reaction material through silica (7 x 4 cm i.d., BIOTAGE, KP-SIL, 60 angstroms) using ethylacetate-hexane (1:4) afforded 470 mg of the desired product, *N*-(*trans*-4-methylcyclohexyl)-2-quinoxalinecarboxamide. Thin-layer
30 chromatography (TLC, silica) using ethylacetate-hexane (1:4) showed a single UV active component at R_f 0.19. GC/EI-MS gave *m/z* (rel. int.) 269 (M⁺, 39), 212 (8), 198 (6), 174 (15), 157 (21), 129 (100), 112 (43), and 102 (46).

-27-

EXAMPLE 2: Preparation of 6-Quinolyl 1-adamantanecarboxylate (41)

1-Adamantanecarbonyl chloride (1.37 g, 6.90 mmol) in pyridine (5 mL) was added to a solution of 6-hydroxyquinoline (1.00 g, 6.89 mmol) in pyridine (15 mL). The reaction was stirred for 16 h. To the stirring reaction mixture was
5 added water (200 mL) which caused the product to precipitate. This precipitate was filtered, washed with water (3 x 50 mL), and dried under high vacuum. This provided 1.56 g (73.7%) of (41) as a light-brown powder:

rt=11.41 min.; m/z (rel. int.) 307 (M+,2), 136 (11), 135 (100), 116 (11), 107 (7), 93 (14), 92 (2), 91 (8), 89 (7), 79 (16), 77 (8).

EXAMPLE 3: Preparation of 1-Adamantyl 6-quinolinecarboxylate (61)**6-Quinolinecarbonyl chloride hydrochloride**

6-Quinolinecarboxylic acid was refluxed in thionyl chloride for 30 min.
15 The excess thionyl chloride was then removed by rotary evaporation (90° C) to provide 6-quinolinecarbonyl chloride hydrochloride.

1-Adamantyl 6-quinolinecarboxylate (61)

6-Quinolinecarbonyl chloride hydrochloride (0.76g, 3.3 mmol) in
20 pyridine (2 mL) was added to a solution of 1-adamantanol (0.60 g, 3.9 mmol) in pyridine (8 mL). The reaction was stirred at 70°C for 16 h. To the stirring reaction mixture was added water (100 mL) which caused the product to precipitate. This precipitate was filtered and then washed with water (3 x 25 mL). The filter cake was dissolved in ethanol (20 mL) and water was then
25 added to the cloud point (16 mL). The crystallizing solution was allowed to stand for 15 h. Filtering and drying under high vacuum for 7 h provided 0.32 g (26%) of (61) as light brown needle-like crystals:

rt=11.48 min.; m/z (rel. int.) 307 (M+,99), 306 (92), 262 (15), 174 (12), 173 (13), 157 (10), 156 (88), 135 (81), 134 (33), 129 (13), 128 (100), 127 (10), 119 (11), 107 (18), 102 (16), 101 (37), 93 (51), 92 (76), 91 (35), 81 (14), 79 (55),
30 78 (15), 77 (49), 75 (17), 67 (24), 55 (18), 53 (13), 51 (13), 41 (31).

In a similar manner, the following alkyl 6-quinoline- and 2-quinoxalinecarboxylates were prepared:

35

- 28 -

2,2,3,3,4,4,5,5-Octafluoro-1-pentyl-6-quinoline-carboxylate hydrochloride (68)

Prepared from 6-quinolinecarbonyl chloride hydrochloride (0.75 g, 3.3 mmol), 2,2,3,3,4,4,5,5-octafluoro-1-pentanol (0.60 mL, 4.3 mmol), pyridine (10 mL), and water (100 mL). Forming the hydrochloride salt with ethereal hydrogen chloride yielded 0.88 g (69%) of (68):

rt=7.11 min.; m/z (rel. int.) 387 (M+,26), 156 (100), 129 (6), 128 (48), 102 (6), 101 (16), 77 (6), 76 (2), 75 (8), 50 (14).

1-Adamantanemethyl 6-quinolinecarboxylate (73)

Prepared from 6-quinolinecarbonyl chloride hydrochloride (0.80 g, 3.5 mmol), 1-adamantanemethanol (0.60 g, 3.6 mmol), pyridine (10 mL), and water (100 mL) yielding 0.75 g (65%) of (73):

rt=11.90 min.; (rel. int.) 321 (M+,35), 320 (12), 263 (15), 156 (30), 148 (23), 136 (11), 135 (100), 129 (9), 128 (52), 107 (15), 106 (7), 105 (9), 102 (7), 101 (16), 93 (34), 92 (20), 91 (20), 81 (11), 80 (7), 79 (40), 78 (6), 77 (24), 75 (7), 67 (14), 55 (9), 53 (6), 51 (6), 41 (14).

1-Adamantyl 2-quinoxalinecarboxylate (92)

Prepared from 2-quinoxaloyl chloride (0.84 g, 4.4 mmol), 1-adamantanol (0.60 g, 3.9 mmol), pyridine (10 mL), and water (100 mL) yielding 0.20 g (16%) of (92):

rt=11.21 min.; m/z (rel. int.) 308 (M+,26), 264 (6), 136 (11), 135 (100), 134 (5), 130 (11), 129 (25), 107 (12), 102 (19), 93 (24), 92 (9), 91 (11), 81 (7), 79 (26), 77 (12), 76 (6), 75 (7), 67 (10), 55 (7), 51 (6), 41 (11).

EXAMPLE 4: Preparation of N-(1-Adamantyl)-3-quinolinecarboxamide (72)

1,1'-Carbonyldiimidazole (161 mg, 1.00 mmol) in *N,N*-dimethylformamide (1 mL) was added in one portion to a suspension of 3-quinolinecarboxylic acid (173 mg, 1.00 mmol) in *N,N*-dimethylformamide (1 mL). The resulting reaction solution was stirred for 2.5 h. 1-Adamantanamine (151 mg, 1.00 mmol) in *N,N*-dimethylformamide (0.5 mL) was added in one portion. The reaction mixture was stirred at 60 °C for 2 h. The reaction was then diluted with chloroform and washed with water (3 x 30 mL). The organic layer was dried (anhydrous magnesium sulfate), filtered through

- 29 -

silica gel, and rotary evaporated. This provided 73 mg (24%) of (72) as a crystalline solid:

rt=11.02 min.; m/z (rel. int.) 306 (M+, 78), 305 (42), 250 (19), 249 (100), 213 (7), 173 (5), 157 (10), 156 (89), 129 (12), 128 (92), 102 (5), 101 (36), 94 (6), 93 (10), 92 (12), 91 (14), 79 (10), 77 (14), 77 (14), 75 (10), 67 (7), 41 (11).

In a similar manner, the following *N*-alkyl-2-quinoline- and 2-quinoxalinecarboxamides were prepared:

10 *N*-(1-Adamantyl)-2-quinolinecarboxamide (74)

Prepared from 1,1'-carbonyldiimidazole (160 mg, 0.987 mmol), quinaldic acid (173 mg, 1.00 mmol), and *N,N*-dimethylformamide (2.5 mL) yielding 77 mg (25%) of (74):

15 rt=10.53 min.; m/z (rel. int.) 306 (M+, 91), 305 (26), 277 (9), 263 (9), 221 (11), 172 (9), 171 (73), 145 (15), 144 (60), 143 (15), 136 (11), 135 (100), 128 (36), 117 (19), 116 (27), 107 (20), 105 (8), 101 (10), 93 (42), 91 (30), 89 (14), 81 (13), 79 (55), 77 (37), 67 (18), 65 (11), 55 (12), 53 (10), 41 (18).

N-(2-Adamantyl)-2-quinoxalinecarboxamide (144)

20 Prepared from 1,1'-carbonyldiimidazole (161 mg, 1.00 mmol), 2-quinoxalinecarboxylic acid (174 mg, 1.00 mmol), 2-adamantanamine (136 mg, 0.90 mmol), and dichloromethane (3.5 mL) yielding 98 mg (35%) of (144):

25 rt=11.79 min.; m/z (rel. int.) 307 (M+, 33), 151 (12), 150 (100), 130 (24), 129 (35), 103 (11), 102 (20), 91 (13), 79 (11), 77 (8), 76 (6), 75 (5), 70 (6), 67 (5), 41 (6).

N-[(1*R*,2*R*,3*R*,5*S*)-3-Pinanemethyl]-2-quinoxalinecarboxamide (151)

30 Prepared from 1,1'-carbonyldiimidazole (161 mg, 1.00 mmol), 2-quinoxalinecarboxylic acid (174 mg, 1.00 mmol), (-)-3-pinanemethylamine (150 mg, 0.90 mmol), and dichloromethane (3.5 mL) yielding 50 mg (17%) of (151):

35 rt=11.46 min.; m/z (rel. int.) 323 (M+, 7), 187 (76), 186 (10), 174 (25), 166 (15), 158 (44), 157 (20), 144 (6), 131 (10), 130 (78), 129 (100), 107 (8), 103 (21), 102 (44), 95 (15), 93 (10), 91 (9), 81 (11), 79 (13), 77 (12), 76 (14), 75 (11), 69 (8), 67 (17), 55 (20), 53 (10), 51 (7), 43 (10), 41 (30).

- 30 -

EXAMPLE 5: Preparation of *N*-(1-Adamantyl)-2-quinoxalinecarboxamide (91)

2-Quinoxaloyl chloride (0.84 g, 4.4 mmol) was added to a solution of 1-
5 adamantanamine (0.60 g, 4.0 mmol) in pyridine (10 mL). The reaction was then
stirred for 30 min. To the stirring reaction mixture was added water (100 mL)
which caused the product to precipitate. This precipitate was filtered, washed
with water (3 x 25 mL), and dried under high vacuum for 16 h. This provided
1.00 g (82%) of (91):

10 rt=11.73 min.; m/z (rel. int.) 307 (M+,39), 279 (5), 157 (5), 151 (11), 150
(100), 130 (21), 129 (58), 103 (12), 102 (24), 94 (7), 93 (8), 91 (10), 79 (9), 77
(9), 76 (7), 75 (6), 67 (5), 41 (8), 41 (8).

In a similar manner, the following *N*-substituted 6-quinoline- and 2-
15 quinoxalinecarboxamides were prepared:

***N*-(1-Adamantyl)-6-quinolinecarboxamide (42)**

Prepared from 6-quinolinecarbonyl chloride hydrochloride (1.51 g,
10 mmol), 1-adamantanamine (1.73 g, 10 mmol), pyridine (5 mL), and water
20 (200 mL) yielding 330 mg (11%) of (42):

rt=11.04 min.; m/z (rel. int.) 306 (M+,34), 305 (15), 250 (11), 249 (56), 156
(11), 155 (100), 130 (5), 128 (10), 127 (69), 126 (5), 102 (8), 101 (16), 93 (8),
92 (9), 91 (12), 79 (10), 77 (16), 67 (6), 41 (11), 41 (11).

25 ***N*-(*exo*-2-Norbornanyl)-2-quinoxalinecarboxamide (148)**

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), *exo*-2-
aminonorbornane (133 mg, 0.90 mmol), pyridine (5 mL), and water (50 mL)
yielding 35 mg (15%) of (148):

30 rt=10.22 min.; m/z (rel. int.) 267 (M+,36), 198 (10), 158 (7), 157 (9), 131 (7),
130 (47), 129 (78), 111 (8), 111 (8), 110 (100), 103 (16), 102 (39), 77 (5), 76
(12), 75 (11), 67 (11), 51 (7), 41 (10).

***N*-[(1*R*,2*S*,4*S*)-Bornyl]-2-quinoxalinecarboxamide (150)**

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), (*R*)-(+)-
35 bornylamine (138 mg, 0.90 mmol), pyridine (5 mL), and water (50 mL) yielding
140 mg (50%) of (150):

rt=10.79 min.; m/z (rel. int.) 309 (M+,27), 199 (8), 187 (10), 174 (10), 158
(11), 157 (14), 153 (10), 152 (82), 144 (9), 135 (11), 131 (7), 130 (51), 129

- 31 -

(100), 109 (20), 103 (18), 102 (43), 95 (38), 93 (12), 91 (7), 79 (9), 77 (11), 76 (13), 75 (11), 67 (17), 55 (14), 53 (8), 51 (8), 43 (8), 41 (25).

***N*-(3-Noradamantyl)-2-quinoxalinecarboxamide (152)**

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), 3-noradamantanamine (157 mg, 0.90 mmol), pyridine (5 mL), and water (50 mL) yielding 167 mg (63%) of (152):

rt=11.00 min.: m/z (rel. int.) 293 (M+,50), 265 (12), 250 (18), 232 (6), 222 (20), 157 (12), 144 (6), 137 (7), 136 (64), 131 (6), 130 (35), 130 (35), 129 (100), 103 (19), 102 (35), 94 (15), 91 (6), 80 (6), 79 (11), 77 (11), 76 (12), 75 (9), 67 (6), 53 (6), 51 (6), 41 (13).

***N*-[(1*R*,2*R*,3*R*,5*S*)-Isopinocampheyl]-2-quinoxalinecarboxamide (165)**

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), (1*R*,2*R*,3*R*,5*S*)-(-)-isopinocampheylamine (138 mg, 0.90 mmol), pyridine (5 mL), and water (50 mL) yielding 230 mg (83%) of (165):

rt=10.88 min.: m/z (rel. int.) 309 (M+,4), 226 (19), 200 (17), 199 (5), 198 (7), 186 (9), 175 (7), 174 (16), 158 (6), 157 (14), 152 (6), 130 (42), 129 (100), 103 (16), 102 (42), 102 (42), 95 (13), 93 (10), 79 (6), 77 (7), 76 (11), 75 (9), 67 (7), 55 (12), 53 (6), 51 (5), 43 (5), 41 (18).

***N*-[(1*S*,2*S*,3*S*,5*R*)-Isopinocampheyl]-2-quinoxalinecarboxamide (166)**

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), (1*S*,2*S*,3*S*,5*R*)-(+)-isopinocampheylamine (138 mg, 0.90 mmol), pyridine (5 mL), and water (50 mL) yielding 208 mg (75%) of (166):

rt=10.88 min.: m/z (rel. int.) 309 (M+,4), 226 (16), 200 (14), 198 (7), 186 (8), 175 (6), 174 (14), 158 (5), 156 (13), 130 (42), 130 (42), 129 (100), 103 (18), 102 (46), 95 (11), 93 (10), 91 (5), 79 (5), 77 (8), 76 (12), 75 (11), 67 (8), 55 (13), 53 (6), 51 (6), 43 (6), 41 (20).

***N*-(5-Chlorotricyclo[2.2.1.0(2,6)]hept-3-yl)-2-quinoxalinecarboxamide (167)**

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), 5-chlorotricyclo[2.2.1.0(2,6)]hept-3-ylamine (129 mg, 0.90 mmol), pyridine (5 mL), and water (50 mL) yielding 100 mg (37%) of (167):

rt=11.29 min.: m/z (rel. int.) 299 (M+,2), 264 (76), 246 (12), 199 (7), 198 (47), 186 (16), 185 (6), 144 (6), 142 (16), 130 (30), 129 (100), 106 (15), 103 (20), 102 (55), 102 (55), 91 (24), 80 (7), 79 (18), 78 (6), 77 (18), 76 (19), 75 (19), 65 (10), 53 (6), 52 (6), 51 (14), 50 (7).

- 32 -

N-(Tricyclo[4.3.1.1(3,8)]undec-3-yl)-2-quinoxalinecarboxamide (168)

Prepared from 2-quinoxaloyl chloride (135 mg, 0.70 mmol), tricyclo[4.3.1.1(3,8)]undec-3-ylamine hydrochloride (100 mg, 0.60 mmol), pyridine (5 mL), and water (50 mL) yielding 110 mg (57%) of (168):

5 $rt=12.52$ min.: m/z (rel. int.) 321 ($M+$, 48), 165 (13), 164 (100), 157 (9), 131 (8), 130 (32), 130 (32), 129 (79), 107 (5), 106 (5), 105 (11), 103 (17), 102 (31), 94 (9), 93 (8), 92 (9), 91 (15), 81 (6), 80 (7), 79 (16), 77 (10), 76 (9), 75 (7), 67 (8), 55 (5), 53 (5), 41 (10).

10 *N*-[(1*S*,2*R*,5*S*)-*cis*-Myrtanyl]-2-quinoxalinecarboxamide (169)

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), (-)-*cis*-myrtanylamine (138 mg, 0.90 mmol), pyridine (5 mL), and water (50 mL) yielding 224 mg (81%) of (169):

15 $rt=11.32$ min.: m/z (rel. int.) 309 ($M+$, 18), 186 (30), 174 (20), 158 (12), 157 (27), 152 (16), 131 (6), 130 (47), 130 (47), 129 (100), 121 (5), 103 (17), 102 (45), 93 (12), 91 (6), 81 (11), 79 (12), 77 (10), 76 (13), 75 (11), 69 (13), 67 (15), 55 (8), 54 (6), 53 (8), 51 (7), 43 (6), 41 (26).

N-[(1*R*,2*R*,4*S*)-Isobornyl]-2-quinoxalinecarboxamide (170)

20 Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), (*R*)-(-)-isobornylamine (138 mg, 0.90 mmol), pyridine (5 mL), and water (50 mL) yielding 130 mg (81%) of (170):

25 $rt=10.76$ min.: m/z (rel. int.) 309 ($M+$, 24), 199 (7), 197 (6), 187 (8), 174 (8), 158 (9), 157 (12), 153 (7), 152 (58), 144 (9), 135 (8), 130 (46), 129 (100), 109 (14), 103 (21), 102 (48), 95 (31), 93 (10), 91 (7), 79 (8), 77 (10), 76 (13), 75 (12), 67 (15), 55 (12), 53 (7), 51 (6), 43 (6), 41 (18).

N-[*endo*-(±)-2-Norbornanyl]-2-quinoxalinecarboxamide (171)

30 Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), *endo*-(±)-2-aminonorbornane (133 mg, 0.90 mmol), pyridine (5 mL), and water (50 mL) yielding 175 mg (73%) of (171):

35 $rt=10.15$ min.: m/z (rel. int.) 267 ($M+$, 35), 198 (11), 185 (6), 158 (7), 157 (11), 144 (5), 131 (7), 130 (55), 129 (100), 111 (6), 110 (81), 103 (24), 102 (56), 77 (7), 76 (19), 75 (17), 75 (17), 67 (13), 55 (5), 53 (7), 51 (9), 50 (5), 41 (14).

N-[(*R*)-2-Phenyl-1-propyl]-2-quinoxalinecarboxamide (172)

Prepared from 2-quinoxaloyl chloride (0.47 g, 2.4 mmol), (*R*)-2-phenyl-1-propylamine (0.30 g, 2.2 mmol), pyridine (5 mL), and water (50 mL) yielding 0.49 g (76%) of (172):

5 *rt*=10.63 min.: *m/z* (rel. int.) 291 (*M*+, 14), 186 (9), 158 (5), 157 (32), 130 (25), 129 (100), 118 (22), 105 (24), 104 (5), 103 (21), 102 (48), 91 (9), 79 (11), 78 (6), 77 (18), 76 (13), 75 (13), 75 (13), 51 (9).

N-[(*S*)-2-Phenyl-1-propyl]-2-quinoxalinecarboxamide (173)

10 Prepared from 2-quinoxaloyl chloride (0.47 g, 2.4 mmol), (*S*)-2-phenyl-1-propylamine (0.30 g, 2.2 mmol), pyridine (5 mL), and water (50 mL) yielding 0.48 g (74%) of (173):

15 *rt*=10.72 min.: *m/z* (rel. int.) 291 (*M*+, 13), 186 (68), 158 (5), 157 (37), 130 (21), 129 (100), 118 (29), 105 (21), 103 (16), 102 (37), 91 (7), 79 (10), 77 (15), 76 (11), 75 (10), 51 (9), 51 (9).

N-(2-Indanyl)-2-quinoxalinecarboxamide (221)

20 Prepared from 2-quinoxaloyl chloride (0.32 g, 1.7 mmol), 2-aminoindan (0.20 g, 1.5 mmol), pyridine (3 mL), and water (30 mL) yielding 0.23 g (53%) of (221):

rt=11.33 min.: *m/z* (rel. int.) 289 (*M*+, 10), 132 (6), 130 (28), 129 (41), 117 (15), 116 (100), 115 (37), 104 (7), 103 (26), 102 (37), 91 (7), 78 (7), 77 (13), 76 (16), 75 (14), 51 (9), 51 (9), 50 (5).

N-Cyclooctyl-2-quinoxalinecarboxamide (228)

25 Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), cyclooctylamine (123 μ L, 114 mg, 0.90 mmol), pyridine (5 mL), and water (100 mL) yielding 100 mg (39%) of (228):

30 *rt*=10.86 min.: *m/z* (rel. int.) 283 (*M*+, 27), 212 (6), 199 (9), 198 (20), 198 (20), 185 (16), 184 (6), 174 (8), 157 (15), 144 (7), 131 (6), 130 (48), 129 (100), 126 (42), 103 (20), 102 (50), 76 (13), 75 (12), 67 (6), 56 (7), 55 (9), 51 (6), 43 (6), 41 (16).

N-Cycloheptyl-2-quinoxalinecarboxamide (229)

35 Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), cycloheptylamine (115 μ L, 102 mg, 0.90 mmol), pyridine (5 mL), and water (100 mL) yielding 30 mg (12%) of (229):

- 34 -

rt=10.30 min.: m/z (rel. int.) 269 (M+,39), 212 (6), 198 (20), 185 (13), 174 (14), 174 (14), 157 (20), 131 (7), 130 (49), 129 (100), 112 (44), 103 (23), 102 (51), 76 (15), 75 (13), 56 (6), 55 (8), 51 (7), 42 (5), 41 (15).

5 ***N*-[2-Spiro(4.5)decyl]-2-quinoxalinecarboxamide (236)**

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), 2-aminospiro(4.5)decane (150 mg, 0.79 mmol), pyridine (5 mL), and water (100 mL) yielding 206 mg (74%) of (236): rt=10.94 min.:

10 m/z (rel. int.) 282 (M+,25), 199 (7), 186 (6), 157 (10), 130 (32), 129 (96), 125 (40), 110 (10), 109 (100), 108 (15), 103 (14), 102 (55), 98 (6), 97 (27), 96 (25), 84 (9), 82 (18), 76 (15), 75 (16), 70 (55), 69 (7), 68 (13), 56 (7), 55 (8), 53 (6), 51 (9), 43 (8), 42 (36), 41 (14).

15 **EXAMPLE 6: Preparation of 1-Adamantanemethyl 6-quinolyl ether (94)**

A mixture of 1-adamantanemethanol (5.00 g, 30.0 mmol) and 6-hydroxyquinoline (13.1 g, 90.2 mmol) in tetrahydrofuran (75 mL) was stirred for 15 min. Then, triphenylphosphine (10.2 g, 39.0 mmol) was added, followed by diethyl azodicarboxylate (6.14 mL, 39.0 mmol). The reaction mixture was 20 refluxed for 18 h. The solvent was then removed by rotary evaporation. The resulting gel was filtered through paper with diethyl ether (3 x 25 mL). The filtrate was rotary evaporated, and the resulting gel was filtered through paper with hexanes (3 x 25 mL). Again the filtrate was rotary evaporated, the resulting gel was filtered through paper with hexanes (3 x 25 mL), and the filtrate was 25 rotary evaporated. This provided 3.8 g (43%) of crude product as a red oil. This oil was chromatographed (2:1 hexanes/ethyl acetate) to provide 1.6 g (18%) of (94):

30 rt=11.29 min.; m/z (rel. int.) 293 (M+,15), 149 (100), 145 (6), 128 (13), 121 (6), 116 (12), 116 (12), 107 (17), 93 (29), 91 (18), 89 (10), 81 (16), 79 (25), 77 (17), 67 (14), 65 (5), 55 (8), 53 (6), 41 (14).

EXAMPLE 7: Preparation of 1-Adamantyl 3-quinolinecarboxylate (101)

A mixture of 1-adamantanol (152 mg, 1.0 mmol), 3-quinolinecarboxylic 35 acid (173 mg, 1.0 mmol), and dimethylaminopyridine (122 mg, 1.0 mmol) in dichloromethane (2 mL) and *N,N*-dimethylformamide (2 mL) was cooled to 0 °C. 1,3-Dicyclohexylcarbodiimide (227 mg, 1.1 mmol) in dichloromethane (1 mL) was added in one portion. The reaction mixture was stirred at 25 °C for 20 h.

- 35 -

The reaction mixture was then diluted with dichloromethane (40 mL) and washed with 1 M sodium hydroxide (3 x 30 mL). The organic layer was dried (anhydrous magnesium sulfate), filtered through Celite, and rotary evaporated. The resulting material was purified by spinning thin-layer chromatography (3% methanol in chloroform). The purest fraction was rotary evaporated, and the resulting material was recrystallized from ethanol. This provided 42 mg (14%) of (101):

rt=7.78 min.: m/z (rel. int.) 307 (M+, 96), 306 (100), 173 (11), 155 (38), 135 (6), 127 (55), 119 (6), 106 (9), 100 (23), 93 (25), 92 (33), 91 (14), 78 (23), 77 (6), 76 (13), 74 (8), 67 (9), 54 (7), 41 (12).

EXAMPLE 8: Preparation of *N*-(α,α -Dimethylphenethyl)-2-quinoxalinecarboxamide (108)

2-Quinoxaloyl chloride (207 mg, 1.07 mmol) in dichloromethane (1 mL) was added to a solution of phentermine (160 mg, 1.07 mmol) in dichloromethane (3 mL) cooled to 0 °C. The reaction was allowed to warm to 25 °C. After 5 min, the reaction mixture was diluted with ethyl acetate (40 mL) and washed with 1 M sodium hydroxide (2 x 40 mL). The organic layer was dried (anhydrous magnesium sulfate), filtered through silica gel, and rotary evaporated. This provided 51 mg (16%) of (108):

rt=9.31 min.: m/z (rel. int.) 305 (M+, 100), 214 (96), 186 (30), 157 (16), 130 (22), 129 (100), 103 (10), 102 (31), 92 (4), 91 (47), 76 (5), 75 (5), 65 (10).

25 *N*-(2-Chlorobenzyl)-2,4,6-triphenylpyridinium tetrafluoroborate

2-Chlorobenzylamine (2.0 g, 14 mmol) was added dropwise to a suspension of 2,4,6-triphenylpyrylium tetrafluoroborate (5.1 g, 13 mmol) in dichloromethane (40 mL). The reaction mixture was stirred for 16 h. Ethanol (4 mL) and excess diethyl ether were added to precipitate the product. The precipitate was filtered and dried. This provided 6.14 g (92%) of *N*-(2-chlorobenzyl)-2,4,6-triphenylpyridinium tetrafluoroborate.

1-(2-Chlorophenyl)-2-methyl-2-nitropropane

2-Nitropropane (3.19 mL, 35.5 mmol) was added to a mixture of sodium hydride (0.85 g, 35 mmol) in methanol (15 mL) cooled to 0 °C. The reaction mixture was then stirred and allowed to warm to 25 °C for 10 min. The solvent

-36-

was rotary evaporated to provide a white solid. A mixture of this solid and *N*-(2-chlorobenzyl)-2,4,6-triphenylpyridinium tetrafluoroborate (6.14 g, 11.8 mmol) in dimethyl sulfoxide (45 mL) was stirred under nitrogen gas for 16 h. Water was then added to quench the reaction. This mixture was then extracted with diethyl ether (3 x 100 mL). The organic layer was washed with saturated aqueous sodium chloride, dried (anhydrous sodium sulfate), and filtered. The filtrate was stirred in strongly acidic Amberlyst 15 ion-exchange resin (1 g/mmol) for 4 h. The reaction mixture was filtered and rotary evaporated. This provided 2.35 g (93%) of 1-(2-chlorophenyl)-2-methyl-2-nitropropane.

10

α,α -Dimethyl-2-chlorophenethylamine

A mixture of Raney nickel (50% by weight in water; 2.3 g) and 1-(2-chlorophenyl)-2-methyl-2-nitropropane (2.35 g, 11 mmol) in ethanol (35 mL) was shaken under hydrogen gas (60 psig) for 3.5 h. The reaction mixture was then filtered, and the filtrate was rotary evaporated. This provided 2.3 g (110%) of α,α -dimethyl-2-chlorophenethylamine.

15

N-(α,α -Dimethyl-2-chlorophenethyl)-2-quinoxalinecarboxamide (197)

In a similar manner to (108), (197) was prepared from 2-quinoxaloyl chloride (158 mg, 0.82 mmol), α,α -dimethyl-2-chlorophenethylamine (151 mg, 0.82 mmol), and dichloromethane (3 mL) yielding 196 mg (70%) of (197):
rt=10.04 min.; m/z (rel. int.) 339 (M+..0), 213 (58), 186 (24), 156 (12), 129 (25), 128 (100), 126 (14), 124 (44), 102 (14), 101 (38), 98 (5), 90 (5), 88 (18), 75 (10), 75 (10), 75 (9), 62 (5), 50 (5), 41 (9).

25

EXAMPLE 9: Preparation of *N*-(α,α -Dimethyl-4-fluorophenethyl)-2-quinoxalinecarboxamide (129)

To a solution of 1-(4-fluorophenyl)-2-methyl-2-propylamine (105 mg, 0.628 mmol) in pyridine (2 mL) was added 2-quinoxaloyl chloride (133 mg, 0.691 mmol). The reaction was then stirred for 30 min. To the stirring reaction mixture was added water (20 mL) which caused the product to separate as an oil. This mixture was extracted with ethyl acetate (1 x 10 mL), washed with water (2 x 5 mL), dried (anhydrous magnesium sulfate), rotary evaporated, and put under high vacuum for 15 h. This provided 146 mg (71.9%) of (129):

35

- 37 -

rt=10.45 min.; m/z (rel. int.) 323 (M+, .1), 214 (73), 186 (22), 157 (14), 135 (4), 130 (19), 129 (100), 109 (22), 103 (9), 102 (30), 83 (7), 76 (9), 75 (8), 42 (6).

5 In a similar manner, the following *N*-substituted 2-quinoxalinecarboxamides were prepared:

N-(β -Methylphenethyl)-2-quinoxalinecarboxamide (131)

Prepared from 2-quinoxaloyl chloride (193 mg, 0.84 mmol), β -methylphenethylamine (103 mg, 0.76 mmol), and pyridine (2 mL) yielding 154 mg (69%) of (131):

rt=10.71 min.; m/z (rel. int.) 291 (M+, .12), 186 (66), 158 (5), 157 (37), 130 (20), 129 (100), 118 (28), 105 (21), 103 (17), 102 (37), 91 (7), 79 (10), 78 (5), 77 (15), 76 (11), 75 (10), 51 (10), 51 (10).

N-(3-Methylcyclohexyl)-2-quinoxalinecarboxamide (161)

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), 3-methylcyclohexylamine (119 mg, 0.90 mmol), and pyridine (5 mL) yielding 190 mg (78%) of (161):

20 rt=9.99 min.; m/z (rel. int.) 269 (M+, .37), 226 (6), 198 (11), 174 (23), 157 (23), 131 (7), 130 (44), 129 (100), 113 (5), 112 (59), 103 (20), 102 (41), 95 (5), 81 (6), 76 (15), 75 (12), 56 (5), 55 (9), 51 (7), 41 (15), 41 (15).

N-(2,3-Dimethylcyclohexyl)-2-quinoxalinecarboxamide (163)

25 Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), 2,3-dimethylcyclohexylamine (115 mg, 0.90 mmol), and pyridine (5 mL) yielding 150 mg (59%) of (163):

30 rt=10.12 min.; m/z (rel. int.) 283 (M+, .35), 212 (6), 198 (14), 175 (6), 174 (39), 158 (7), 157 (22), 131 (6), 130 (46), 129 (100), 126 (44), 109 (8), 103 (20), 103 (20), 102 (45), 76 (13), 75 (11), 67 (7), 56 (10), 55 (12), 51 (6), 43 (6), 41 (16).

N-[(1*S*,2*S*,3*S*,5*R*)-3-Pinanemethyl]-2-quinoxalinecarboxamide (207)

35 Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), (+)-3-pinanemethylamine (150 mg, 0.90 mmol), and pyridine (5 mL) yielding 229 mg (79%) of (207):

rt=12.07 min.; m/z (rel. int.) 323 (M+, .12), 187 (100), 186 (12), 174 (33), 166 (24), 159 (8), 158 (66), 157 (26), 150 (9), 144 (7), 131 (11), 130 (80), 129 (85),

- 36 -

107 (10), 103 (14), 102 (31), 95 (22), 93 (11), 91 (8), 83 (7), 81 (11), 79 (11), 77 (8), 76 (8), 69 (8), 67 (13), 55 (17), 43 (9), 41 (25).

EXAMPLE 10: *N*-(1-Adamantanemethyl)-2-quinoxalinecarboxamide
(146)

2-Quinoxaloyl chloride (429 mg, 2.6 mmol) was added to a solution of 1-adamantanemethylamine (500 mg, 2.6 mmol) in chloroform (5 mL). The reaction mixture was heated until everything had dissolved. The reaction mixture
10 was stirred at 25 °C for 1 h. To the stirring reaction mixture was added water (100 mL) which caused the product to precipitate. The precipitate was filtered, washed with water (2x), and dried under high vacuum. This provided 375 mg (45%) of (146):

rt=12.27 min.; m/z (rel. int.) 321 (M+,101), 186 (7), 174 (6), 164 (34), 158
15 (6), 157 (8), 136 (11), 135 (100), 131 (7), 130 (46), 129 (75), 107 (23), 105 (6), 103 (20), 102 (53), 93 (44), 92 (6), 91 (23), 81 (13), 79 (47), 77 (24), 76 (16), 75 (13), 67 (16), 65 (6), 55 (9), 53 (8), 51 (8), 41 (13).

EXAMPLE 11: Preparation of *N*-(4-Methylcyclohexyl)-2-quinoxalinecarboxamide (162)

To a solution of 4-methylcyclohexylamine (119 mg, 0.90 mmol) in pyridine (2 mL) was added 2-quinoxaloyl chloride (193 mg, 1.0 mmol). The reaction was then stirred for 1 h. To the stirring reaction mixture was added
25 water (20 mL) which caused the product to precipitate as an oil. This mixture was extracted with 30% dichloromethane in diethyl ether (2 x 25 mL), washed with water (2 x 25 mL), dried (anhydrous sodium sulfate), and rotary evaporated. This provided 123 mg (51%) of (162):

rt=10.00 min.; m/z (rel. int.) 269 (M+,53), 212 (15), 212 (15), 198 (7), 174
30 (25), 158 (6), 157 (36), 131 (7), 130 (44), 129 (100), 113 (6), 112 (66), 103 (18), 102 (36), 95 (9), 81 (6), 76 (12), 75 (9), 56 (5), 55 (10), 51 (6), 41 (12).

EXAMPLE 12: Preparation of *N*-[(1*S*,2*S*,5*S*)-*trans*-Myrtanyl]-2-quinoxalinecarboxamide (225)

(1*S*,2*S*,5*S*)-*trans*-Myrtanyl trifluoroacetate

Trifluoroacetic anhydride (5.50 mL, 39.0 mmol) was added to (-)-*trans*-myrtanol (5.10 mL, 32.5 mmol) in dry tetrahydrofuran (100 mL). This reaction

- 39 -

mixture was stirred for 1 h. The reaction mixture was rotary evaporated. This provided 7.60 g (94%) of (1*S*,2*S*,5*S*)-*trans*-myrtanyl trifluoroacetate.

(1*R*,2*R*,5*R*)-*trans*-Myrtanyl trifluoroacetate

5 In a similar manner, (1*R*,2*R*,5*R*)-*trans*-myrtanyl trifluoroacetate was prepared from trifluoroacetic anhydride (5.40 mL, 38.0 mmol, 1.2 equiv) (+)-*trans*-myrtanol (5.00 mL, 4.90 g, 31.7 mmol), and tetrahydrofuran (100 mL) yielding 7.60 g (94%) of (1*R*,2*R*,5*R*)-*trans*-myrtanyl trifluoroacetate.

10 **(1*S*,2*S*,5*S*)-*trans*-Myrtanylazide**

A mixture of (1*S*,2*S*,5*S*)-*trans*-myrtanyl trifluoroacetate (1.0 g, 4.0 mmol), sodium azide (0.39 g, 6.0 mmol), and *N,N*-dimethylformamide (50 mL) was stirred at 80 °C for 24 h. After cooling to 25 °C, water (100 mL) was added, and this mixture was extracted with diethyl ether (2 x 50 mL). The
15 organic layer was then dried (anhydrous sodium sulfate) and rotary evaporated. This provided 1.12 g (100%) of (1*S*,2*S*,5*S*)-*trans*-myrtanylazide as a colorless oil.

(1*R*,2*R*,5*R*)-*trans*-Myrtanylazide

20 In a similar manner, (1*R*,2*R*,5*R*)-*trans*-myrtanylazide was prepared from (1*R*,2*R*,5*R*)-*trans*-myrtanyl trifluoroacetate (7.60 g, 30.4 mmol), sodium azide (3.00 g, 45.6 mmol), and *N,N*-dimethylformamide (100 mL) yielding 4.10 g (48.2%) of (1*R*,2*R*,5*R*)-*trans*-myrtanylazide.

25 **(1*S*,2*S*,5*S*)-*trans*-Myrtaniline**

A mixture of (1*S*,2*S*,5*S*)-*trans*-myrtanylazide (1.12 g, 7.32 mmol) and platinum(IV) oxide hydrate (0.34 g) in ethanol (50 mL) was shaken under hydrogen gas (50 psig) for 2 h. The reaction mixture was then filtered through paper, and the filtrate was rotary evaporated. The resulting material was taken
30 up in 0.12 M hydrochloric acid (100 mL), and the aqueous solution was washed with diethyl ether (2 x 50 mL). The aqueous layer was made basic with 0.1 M sodium hydroxide (50 mL) and extracted with dichloromethane (2 x 50 mL). The organic layer was then dried (anhydrous sodium sulfate) and rotary

evaporated. This provided 78 mg (7%) of (1*S*,2*S*,5*S*)-*trans*-myrtaniline as a light yellow oil.

(1*R*,2*R*,5*R*)-*trans*-Myrtaniline

5 In a similar manner, (1*R*,2*R*,5*R*)-*trans*-myrtaniline was prepared from (1*R*,2*R*,5*R*)-*trans*-myrtanilazide (4.10 g, 26.8 mmol), platinum(IV) oxide hydrate (0.41 g), and ethanol (75 mL) yielding 2.00 g (48.8%) of (1*R*,2*R*,5*R*)-*trans*-myrtaniline.

10 ***N*-[(1*S*,2*S*,5*S*)-*trans*-Myrtanyl]-2-quinoxalinecarboxamide (225)**

In a similar manner to (162), (225) was prepared from 2-quinoxaloyl chloride (49 mg, 0.25 mmol), (1*S*,2*S*,5*S*)-*trans*-myrtaniline (35 mg, 0.23 mmol), and pyridine (5 mL) yielding 8 mg (10%) of (225):
 15 *rt*=11.23 min.: *m/z* (rel. int.) 309 (*M*+,25), 187 (15), 186 (39), 174 (12), 158 (14), 157 (29), 152 (20), 131 (6), 130 (47), 130 (47), 129 (100), 103 (15), 102 (41), 93 (9), 91 (6), 81 (12), 79 (12), 77 (9), 76 (11), 75 (10), 69 (14), 67 (17), 55 (8), 54 (5), 53 (7), 51 (7), 43 (6), 41 (25).

***N*-[(1*R*,2*R*,5*R*)-*trans*-Myrtanyl]-2-quinoxalinecarboxamide (226)**

20 In a similar manner, (226) was prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), (1*R*,2*R*,5*R*)-*trans*-myrtaniline (138 mg, 0.90 mmol), and pyridine (5 mL) yielding 27 mg (10%) of (226):
rt=11.19 min.: *m/z* (rel. int.) 309 (*M*+,21), 186 (47), 186 (18), 174 (17), 158 (16), 157 (34), 152 (30), 131 (6), 130 (47), 130 (47), 129 (100), 121 (6), 103 (15), 102 (40), 93 (11), 91 (6), 81 (12), 79 (11), 77 (8), 76 (10), 75 (9), 69 (14), 67 (17), 55 (7), 53 (6), 51 (5), 43 (5), 41 (18).

EXAMPLE 13: Preparation of *N*-[*N'*-(*R*)- α -Methylbenzyl-2-acetamido]-3-aminoquinoline dihydrochloride (156)

30

***N*-(*R*)- α -Methylbenzyl-2-chloroacetamide**

(*R*)- α -Methylbenzylamine (2.4 g, 20 mmol) in dichloromethane (50 mL) was added to chloroacetyl chloride (2.25 g, 20 mmol) in dichloromethane (70 mL) and pyridine (10 mL). The reaction solution was stirred, then diluted with diethyl ether (500 mL), washed with water (3 x 30 mL), dried (anhydrous magnesium sulfate), and rotary evaporated. This provided 3.60 g of *N*-(*R*)- α -methylbenzyl-2-chloroacetamide.

***N*-(*R*)- α -Methylbenzyl-2-iodoacetamide**

A solution of sodium iodide (10.37 g, 69 mmol) in dry acetone was slowly added to a solution of *N*-(*R*)- α -methylbenzyl-2-chloroacetamide (3.39 g, 17 mmol) in dry acetone, and the reaction mixture was refluxed for 16 h. The reaction mixture was then filtered, and the filtrate was rotary evaporated. Diethyl ether was added, and the mixture was stirred for 20 min. The mixture was then filtered, and the filtrate was rotary evaporated and then put under high vacuum to provide *N*-(*R*)- α -methylbenzyl-2-iodoacetamide.

***N*-[*N'*-(*R*)- α -Methylbenzyl-2-acetamido]-3-aminoquinoline dihydrochloride (156)**

A mixture of 3-aminoquinoline (0.15 g, 1.0 mmol) and potassium fluoride on Celite (50%) (0.30 g, 2.5 mmol) in acetonitrile (20 mL) was stirred for 1 h. *N*-(*R*)- α -Methylbenzyl-2-iodoacetamide (0.31 g, 1.0 mmol) in acetonitrile was added, and the reaction mixture was refluxed for 64 h. The mixture was filtered, and the filtrate was rotary evaporated. The resulting material was taken up in diethyl ether and washed with 1 M sodium hydroxide (3 x 30 mL). The combined aqueous layers were saturated with sodium chloride and were then extracted with chloroform (4x). The combined organic layer were dried (anhydrous magnesium sulfate) and rotary evaporated. The resulting material was dissolved in chloroform (10 mL), 1 M hydrogen chloride in diethyl ether (5 mL) was added, and the solution was rotary evaporated. The resulting material was dissolved in chloroform (5 mL) and filtered through a 0.45 μ m filter disc, and the filtrate was evaporated. This provided 13 mg (3%) of (156):

rt=10.43 min.; m/z (rel. int.) 328 (M+, 11), 182 (12), 181 (86), 180 (37), 167 (22), 166 (25), 165 (17), 162 (53), 161 (95), 160 (37), 148 (32), 145 (18), 135 (21), 132 (16), 122 (9), 120 (22), 119 (20), 107 (19), 106 (13), 105 (100), 104 (22), 103 (19), 90 (12), 79 (25), 78 (11), 77 (38), 51 (10), 44 (10), 41 (11).

EXAMPLE 14: Preparation of 1-(1-Adamantyl)-2-(benzothiazol-2-ylsulfanyl)ethanone (273)

Sodium hydride (36.5 mg, 1.52 mmol, 60% in mineral oil) was washed with pentane (4X), dried under N₂, suspended in dimethylformamide (DMF, 10

-42-

mL) and cooled to 0 °C. With stirring, a solution of 2-mercaptobenzothiazole (253.3 mg, 1.52 mmol) in DMF (5 mL) was added dropwise. The reaction was stirred 20 minutes at 0°C and treated with a solution of 1-adamantanebromomethyl ketone (389.8 mg, 1.52 mmol) in DMF (8 mL). The reaction was stirred 30 minutes at ambient temperature and diluted with diethyl ether (100 mL). The resulting solution was washed with water (5 x 30 mL) and the remaining organic solution dried over anhydrous MgSO₄, filtered, and concentrated to a solid. Recrystallization from hot ethanol afforded 287 mg (55%) of the desired product: GC/EI-MS gave *m/z* (rel. int.) 343 (M⁺, 10), 315 (2), 180 (2), 148 (10), 135 (100), 107 (9), 93 (17), and 79 (20).

EXAMPLE 15: Assay of mGluR Group I antagonist activity

HEK-293 cells expressing a recombinant receptor as described in WO 97/05252 were loaded with 2 μM Fura-2 acetoxymethylester by incubation for 30-40 minutes at 37 °C in SPF-PCB (126 mM NaCl, 5 mM KCl, 1 mM MgCl₂, 20 mM Na-HEPES, 1.0 mM CaCl₂, 1 mg/mL glucose, and 0.5% BSA, pH 7.4).

The cells were washed 1-2 times in SPF-PCB, resuspended to a density of 4-5 million cells/mL and kept at 37 °C in a plastic beaker. For recording fluorescent signals, the cells were diluted five-fold into a quartz cuvette with BSA-free 37 °C SPF-PCB to achieve a final BSA concentration of 0.1% (1.2 mL of 37 °C BSA-free SPF-PCB + 0.3 mL cell suspension). Measurements of fluorescence were performed at 37 °C with constant stirring using a custom-built spectrofluorimeter (Biomedical Instrumentation Group, University of Pennsylvania). Excitation and emission wavelengths were 340 and 510 nm, respectively. To calibrate fluorescence signals, digitonin (Sigma Chemical Co., St. Louis, MO; catalog # D-5628; 50 μg/mL, final) was added to obtain maximal fluorescence (F_{max}), and the apparent minimal fluorescence (F_{min}) was determined by adding TRIS-Base/EGTA (10 mM, pH 8.3, final). Concentrations of intracellular Ca²⁺ were calculated using a dissociation constant (K_d) of 224 nM and applying the equation:

$$[Ca^{2+}]_i = (F - F_{min} / F_{max}) \times K_d;$$

- 43 -

where F is fluorescence measured at any particular time of interest and F falls between F_{\max} and F_{\min} .

Control responses to the addition of 5 mM Ca^{2+} (final extracellular
5 calcium concentration, 6 mM) were determined in separate cuvettes. Control
responses to changes in extracellular calcium were determined throughout the
length of the experiment. Compounds were tested at a single concentration per
cuvette of cells, and all compounds were prepared in DMSO. Appropriate
dilutions were made such that compounds were added in no greater volume than
10 10 μl per a total volume of 1500 μl (final DMSO not greater than 0.67%) to
achieve any particular testing concentration.

Once a stable intracellular calcium baseline was achieved, the compound
was added to the cuvette. The response or lack of response to the compound
addition was allowed to stabilize for 1-3 minutes and then 5 mM calcium was
15 added to determine the effect of the compound on the subsequent calcium
response. Once the peak for the subsequent calcium response was obtained,
digitonin and EGTA were added in a sequential manner to determine F_{\max} and
 F_{\min} respectively. Data were expressed as changes in intracellular calcium
concentrations in nM. These changes in the calcium response post compound
20 addition were compared to the control (no compound) calcium response.
Responses to calcium in the presence of test compounds were normalized as a
percent change from that of controls. Data were entered into a Levenberg-
Marquardt analysis for non-linear least squares and an IC_{50} and 95% confidence
intervals thereof were determined for each compound.

25 The invention thus has been disclosed broadly and illustrated in reference
to representative embodiments described above. Those skilled in the art will
recognize that various modifications can be made to the present invention without
departing from the spirit and scope thereof.

- 44 -

What is claimed is:

1. A compound represented by the formula I.



wherein R is an optionally substituted straight or branched chain alkyl, aralkyl, cycloalkyl, or alkylcycloalkyl group containing 5-12 carbon atoms,

wherein Ar is an optionally substituted aromatic, heteroaromatic, aralkyl, or heteroaralkyl moiety containing up to 10 carbon atoms and up to 4 heteroatoms, and

wherein [linker] is $-(\text{CH}_2)_n-$, where n is 2-6, and wherein up to 4 CH_2 groups may independently be substituted with groups selected from the group consisting of $\text{C}_1\text{-C}_3$ alkyl, CHOH , CO , O , S , SO , SO_2 , N , NH , and NO , provided that two heteroatoms may not be adjacent except when those atoms are both N or are both NH, and wherein any two adjacent CH_2 groups may be replaced by a substituted or unsubstituted alkene or alkyne group,

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein Ar comprises a ring system selected from the group consisting of benzene, thiazole, furyl, pyranyl, 2H-pyrrolyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, benzothiazole, benzimidazole, 3H-indolyl, indolyl, indazolyl, purinyl, quinoliziny, isoquinolyl, quinolyl, phthaliziny, naphthyridinyl, quinazolinyl, cinnolinyl, isothiazolyl, quinoxalinyl, indoliziny, isoindolyl, benzothienyl, benzofuranyl, isobenzofuranyl, and chromenyl rings,

wherein Ar optionally may independently be substituted with up to two $\text{C}_1\text{-C}_3$ alkyl groups, or up to two halogen atoms, where halogen is selected from F, Cl, Br, and I.

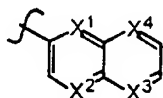
3. The compound according to claim 1, wherein R contains 7-11 carbon atoms, wherein some or all of the hydrogen atoms on two carbon atoms optionally may be replaced with substituents independently selected from the group consisting of F, Cl, OH, OMe, and $=\text{O}$.

- 45 -

4. The compound according to claim 1, wherein [linker] comprises an amide, ester, or thioester group.

5. The compound according to claim 3, wherein R comprises a moiety selected from the group consisting of adamantyl, 2-adamantyl, (1S,2S,3S,5R)-isopinocampheyl, tricyclo[4.3.1.1(3.8)]undec-3-yl, (1S,2R,5S)-*cis*-myrtanyl, (1R,2R,4S)-isobornyl, (1R,2R,3R,5S)-isopinocampheyl, (1S,2S,5S)-*trans*-myrtanyl, (1R,2R,5R)-*trans*-myrtanyl, (1R,2S,4S)-bornyl, 1-adamantanemethyl, 3-noradamantyl, (1S,2S,3S,5R)-3-pinanemethyl, cyclooctyl, α,α -dimethylphenethyl, (S)-2-phenyl-1-propyl, cycloheptyl, 4-methyl-2-hexyl groups, 2,2,3,3,4,4,4-heptafluorobutyl, 4-ketoadamantyl, 3-phenyl-2-methylpropyl, 3,5-dimethyladamantyl, *trans*-2-phenylcyclopropyl, 2-methylcyclohexyl, 3,3,5-trimethylcyclohexyl, 2-(*o*-methoxyphenyl)ethyl, 2-(1,2,3,4-tetrahydronaphthyl), 4-phenylbutyl, 2-methyl-2-phenylbutyl, 2-(*m*-fluorophenyl)ethyl, 2-(*p*-fluorophenyl)ethyl, 2-(3-hydroxy-3-phenyl)propyl, (S)-2-hydroxy-2-phenylethyl, (R)-2-hydroxy-2-phenylethyl, 2-(3-*m*-chlorophenyl-2-methyl)propyl, 2-(3-*p*-chlorophenyl-2-methyl)propyl, 4-*tert*-butyl-cyclohexyl, (S)-1-(cyclohexyl)ethyl, 2-(3-(3,4-dimethylphenyl)-2-methyl)propyl, 3,3-dimethylbutyl, 2-(5-methyl)hexyl, 1-myrtanyl, 2-bornyl, 3-pinanemethyl, 2,2,3,3,4,4,5,5-octafluoropentyl, *p*-fluoro- α,α -dimethylphenethyl, 2-naphthyl, 2-bornanyl, cyclohexylmethyl, 3-methylcyclohexyl, 4-methylcyclohexyl, 3,4-dimethylcyclohexyl, 5-chloro-tricyclo[2.2.1]heptyl, *o*- α,α -dimethylphenethyl, 2-indanyl, 2-spiro[4.5]decyl, 2-phenylethyl, 1-adamantylethyl, 1-(1-bicyclo[2.2.1]hept-2-yl)ethyl, 2-(2-methyl-2-phenyl)propyl, 2-(*o*-fluorophenyl)ethyl, 1-(cyclohexyl)ethyl, and cyclohexyl.

6. The compound according to claim 1, wherein Ar comprises a group having the formula



wherein X^1 , X^2 , X^3 , and X^4 independently can be N or CH, provided that not more than two of X^1 , X^2 , X^3 , and X^4 can be N.

-46-

7. The compound according to claim 6, wherein X^1 is N.
8. The compound according to claim 7, wherein X^2 is N.
9. The compound according to claim 6, wherein X^3 is N.
10. The compound according to claim 6, wherein X^1 is CH and X^3 is N.
11. The compound according to claim 1, wherein Ar is an optionally substituted 2-, 3-, or 4-pyridyl moiety.
12. The compound according to claim 1, wherein Ar is a 6-benzothiazolyl moiety.
13. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable diluent or excipient.
14. A method of making a compound according to claim 4, comprising reacting a compound containing an activated carboxylic acid group with a compound containing an amine, hydroxyl, or thiol group.
15. A method of inhibiting activation of an mGluR Group I receptor, comprising treating a cell containing said receptor with an effective amount of a compound according to claim 1.
16. A method of inhibiting neuronal damage caused by excitatory activation of an mGluR Group I receptor, comprising treating neurons with an effective amount of a compound according to claim 1.
17. A method of treating a disease associated with glutamate-induced neuronal damage, comprising administering to a patient suffering from said disease an effective amount of a composition according to claim 13.

18. The compound according to claim 1, wherein said compound is selected from the group consisting of *N*-[6-(2-Methylquinolyl)]-1-adamantanecarboxamide, *N*-(6-Quinolyl)-1-adamantanecarboxamide, *N*-(2-Quinolyl)-1-adamantanecarboxamide, *N*-(3-Quinolyl)-1-adamantanecarboxamide, 6-Quinolyl-1-adamantanecarboxylate, 1-Adamantyl-6-quinolinecarboxylate, 2,2,3,3,4,4,5,5-Octafluoro-1-pentyl-6-quinolinecarboxylate, 1-Adamantanemethyl-6-quinolinecarboxylate, 1-Adamantyl-2-quinoxalinecarboxylate, *N*-(1-Adamantyl)-3-quinolinecarboxamide, *N*-(1-Adamantyl)-2-quinolinecarboxamide, *N*-(2-Adamantyl)-2-quinoxalinecarboxamide, *N*-[(1*R*,2*R*,3*R*,5*S*)-3-Pinanemethyl]-2-quinoxalinecarboxamide, *N*-(1-Adamantyl)-2-quinoxalinecarboxamide, *N*-(1-Adamantyl)-6-quinolinecarboxamide, *N*-(*exo*-2-Norbornanyl)-2-quinoxalinecarboxamide, *N*-[(1*R*,2*S*,4*S*)-Bornyl]-2-quinoxalinecarboxamide, *N*-(3-Noradamantyl)-2-quinoxalinecarboxamide, *N*-[(1*R*,2*R*,3*R*,5*S*)-Iso-pinocamphenyl]-2-quinoxalinecarboxamide, *N*-[(1*S*,2*S*,3*S*,5*R*)-Isopinocamphenyl]-2-quinoxalinecarboxamide, *N*-(5-Chloro-[2.2.1.0]tricyclo-2,6-hepta-3-yl)-2-quinoxalinecarboxamide, *N*-([4.3.1.1]Tricyclo-3,8-undeca-3-yl)-2-quinoxalinecarboxamide, *N*-[(1*S*,2*R*,5*S*)-cis-Myrtanyl]-2-quinoxalinecarboxamide, *N*-[(1*R*,2*R*,4*S*)-Isobornyl]-2-quinoxalinecarboxamide, *N*-[endo-(±)-2-Norbornanyl]-2-quinoxalinecarboxamide, *N*-[(*R*)-2-Phenyl-1-propyl]-2-quinoxalinecarboxamide, *N*-[(*S*)-2-Phenyl-1-propyl]-2-quinoxalinecarboxamide, *N*-(2-Indanyl)-2-quinoxalinecarboxamide, 1-Adamantanemethyl 6-quinolyl ether, 1-Adamantyl-3-quinolinecarboxylate, *N*-(α,α -Dimethylphenethyl)-2-quinoxalinecarboxamide, *N*-(α,α -Dimethyl-2-chlorophenethyl)-2-quinoxalinecarboxamide, *N*-(α,α -Dimethyl-4-fluorophenethyl)-2-quinoxalinecarboxamide, *N*-(β -Methylphenethyl)-2-quinoxalinecarboxamide, *N*-(3-Methylcyclohexyl)-2-quinoxalinecarboxamide, *N*-(2,3-Dimethylcyclohexyl)-2-quinoxalinecarboxamide, *N*-[(1*S*,2*S*,3*S*,5*R*)-3-Pinanemethyl]-2-quinoxalinecarboxamide, *N*-(1-Adamantanemethyl)-2-quinoxalinecarboxamide, *N*-(4-Methylcyclohexyl)-2-quinoxalinecarboxamide, *N*-[(1*S*,2*S*,5*S*)-*trans*-Myrtanyl]-2-quinoxalinecarboxamide, and *N*-[(1*R*,2*R*,5*R*)-*trans*-Myrtanyl]-2-quinoxalinecarboxamide, and pharmaceutically acceptable salts thereof.

19. The compound according to claim 1, wherein said compound is selected from the group consisting of *N*-(1-Adamantyl)-3-quinolinecarboxamide, *N*-(1-Adamantyl)-2-quinolinecarboxamide, *N*-(2-Adamantyl)-2-quinoxaline-carboxamide, *N*-[(1*R*,2*R*,3*R*,5*S*)-3-Pinanemethyl]-2-quinoxaline-carboxamide, *N*-(1-Adamantyl)-2-quinoxaline-carboxamide, *N*-(1-Adamantyl)-6-quinolinecarboxamide, *N*-(*exo*-2-Norbornanyl)-2-quinoxaline-carboxamide, *N*-[(1*R*,2*S*,4*S*)-Bornyl]-2-quinoxaline-carboxamide, *N*-(3-Noradamantyl)-2-quinoxaline-carboxamide, *N*-[(1*R*,2*R*,3*R*,5*S*)-Isopinocampheyl]-2-quinoxaline-carboxamide, *N*-[(1*S*,2*S*,3*S*,5*R*)-Isopinocampheyl]-2-quinoxaline-carboxamide, *N*-(5-Chloro-[2.2.1.0]tricyclo-2,6-hepta-3-yl)-2-quinoxaline-carboxamide, *N*-[(4.3.1.1]Tricyclo-3,8-undeca-3-yl)-2-quinoxaline-carboxamide, *N*-[(1*S*,2*R*,5*S*)-*cis*-Myrtanyl]-2-quinoxaline-carboxamide, *N*-[(1*R*,2*R*,4*S*)Isobornyl]-2-quinoxaline-carboxamide, *N*-[*endo*-(\pm)-2-Norbornanyl]-2-quinoxaline-carboxamide, *N*-[(1*S*,2*S*,3*S*,5*R*)-3-Pinanemethyl]-2-quinoxalinecarboxamide, *N*-(1-Adamantanemethyl)-2-quinoxalinecarboxamide, *N*-[(1*S*,2*S*,5*S*)-*trans*-Myrtanyl]-2-quinoxalinecarboxamide, and *N*-[(1*R*,2*R*,5*R*)-*trans*-Myrtanyl]-2-quinoxalinecarboxamide, and pharmaceutically acceptable salts thereof.

20. The compound according to claim 1, wherein said compound is selected from the group consisting of *N*-[6-(2-Methylquinolyl)]-1-adamantanecarboxamide, *N*-(6-Quinolyl)-1-adamantanecarboxamide, *N*-(2-Quinolyl)-1-adamantanecarboxamide, and *N*-(3-Quinolyl)-1-adamantanecarboxamide, and pharmaceutically acceptable salts thereof

21. The compound according to claim 1, wherein said compound is selected from the group consisting of *N*-(3-Methylcyclohexyl)-2-quinoxalinecarboxamide, *N*-(2,3-Dimethylcyclohexyl)-2-quinoxalinecarboxamide, *N*-[(1*S*,2*S*,3*S*,5*R*)-3-Pinanemethyl]-2-quinoxalinecarboxamide, *N*-(1-Adamantanemethyl)-2-quinoxalinecarboxamide, and *N*-(4-Methylcyclohexyl)-2-quinoxalinecarboxamide, and pharmaceutically acceptable salts thereof.

22. The compound according to claim 1, wherein said compound is selected from the group consisting of *N*-[(*R*)-2-Phenyl-1-propyl]-2-

quinoxalinecarboxamide, *N*-[(*S*)-2-Phenyl-1-propyl]-2-quinoxalinecarboxamide, *N*-(2-Indanyl)-2-quinoxalinecarboxanride, *N*-(α - α -Dimethylphenethyl)-2-quinoxalinecarboxamide, *N*-(α , α -Dimethyl-2-chlorophenethyl)-2-quinoxalinecarboxamide, *N*-(α , α -Dimethyl-4-fluorophenethyl)-2-quinoxalinecarboxamide, and *N*-(β -Methylphenethyl)-2-quinoxalinecarboxamide, and pharmaceutically acceptable salts thereof.

23. The compound according to claim 1, wherein said compound is 1-Adamantanemethyl 6-quinolyl ether, or a pharmaceutically acceptable salt thereof.

24. The compound according to claim 1, wherein said compound is selected from the group consisting of 6-Quinolyl-1-adamantanecarboxylate, 1-Adamantyl-6-quinolinecarboxylate, 2,2,3,3,4,4,5,5-Octafluoro-1-pentyl 6-quinolinecarboxylate, 1-Adamantanemethyl 6-quinolinecarboxylate, 1-Adamantyl-2-quinoxalinecarboxylate, and 1-Adamantyl-3-quinolinecarboxylate, and pharmaceutically acceptable salts thereof.

25. The compound according to claim 1, wherein said compound is selected from the group consisting of 3-(1-Adamantanemethoxy)-2-chloroquinoxaline, 2-(1-Adamantanemethoxy)-3-methylquinoxaline, 3-(1-Adamantanemethoxy)-2-fluoroquinoxaline, 2-(1-Adamantanemethoxy)-3-trifluoromethylquinoxaline, *N*-[2-(4-Phenylthiazolyl)]-1-adamantanecarboxamide, *N*-[2-(5-Methyl-4-phenylthiazolyl)]-1-adamantanecarboxamide, 1-(1-Adamantyl)-2-(benzothiazol-2-ylsulfanyl)ethanone, *N*-(1-Adamantyl)-2-chloroquinoxaline-3-carboxamide, *N*-(1-Adamantyl)-3-methylquinoxaline-2-carboxamide, and *N*-(1-Adamantyl)-1-oxyquinoxaline-3-carboxamide, and pharmaceutically acceptable salts thereof.

26. The compound according to claim 1, wherein said compound is selected from the group consisting of 4-Chlorophenyl 3-coumarincarboxylate, 2-(1-Adamantanemethylsulfanyl)quinoxaline, 3-(1-Adamantanemethoxy)-2-chloropyrazine, 1-(1-Adamantyl)-2-(4, 6-dimethylpyrimidin-2-

ylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(2-anisylsulfanyl)ethanone, 3-(1-Adamantanemethoxy)-1*H*-quinoxalin-2-one, 1-(1-Adamantyl)-2-(3-anisylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(4-anisylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(4-chlorophenylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(2-naphthylsulfanyl)ethanone, *N*-(2-[6-(1-Piperidinyl)pyrazinyl])-1-adamantanecarboxamide, *N*-(2-[6-(1-Piperidinyl)pyrazinyl])adamantan-1-ylmethylcarboxamide, 1-(1-Adamantyl)-2-(1-naphthylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(8-quinolylsulfanyl)ethanone hydrochloride, 1-(1-Adamantyl)-2-(4-trifluoromethoxyphenoxy)ethanone, 2-(1-Adamantanemethoxy)quinoxaline, *N*-(*trans*-4-Methylcyclohexyl)-2-quinoxalinecarboxamide, *N*-(*cis*-4-Methylcyclohexyl)-2-quinoxalinecarboxamide, *N*-(*trans*-4-Methylcyclohexyl)-2-quinolinecarboxamide, *N*-(*trans*-4-Methylcyclohexyl)-3-quinolinecarboxamide, and *N*-(*trans*-4-Methylcyclohexyl)-6-quinolinecarboxamide, and pharmaceutically acceptable salts thereof.

27. The compound according to claim 1, wherein said compound is selected from the group consisting of 2-(1-Adamantanemethylsulfanyl)-benzothiazole, *N*-(4-Phenylbutyl)-2-quinoxalinecarboxamide, 1-(1-Adamantyl)-2-(4, 6-dimethylpyrimidin-2-ylsulfanyl)ethanol, 1-(1-Adamantyl)-2-(3-chloroquinoxal-2-yl)ethanone, 2-(1-Adamantanemethylsulfanyl)-3-methylquinoxaline, *N*-(1-Adamantyl)-2-anisamide, *N*-(1-Adamantanemethyl)-2-anisamide, 1-(1-Adamantyl)-2-(4-chlorophenylsulfanyl)ethanone, 2-(1-Adamantanemethylsulfonyl)-3-methylquinoxaline, 1-(1-Adamantyl)-2-(4-fluorophenylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(3-fluorophenylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(2-methoxyphenoxy)ethanone, 1-(4-Anisylsulfanyl)butan-2-one, 1-(1-Adamantyl)-2-(4-anisidinyl)ethanone hydrochloride, 3, 3-Dimethyl-1-(4-anisylsulfanyl)butan-2-one, 1-(4-Biphenyl)-2-(4-anisylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(2-trifluoromethoxyphenylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(3-methylquinoxal-2-ylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(2-anisidinyl)ethanone hydrochloride, 1-(1-Adamantyl)-2-(4-trifluoromethoxyphenylamino)ethanone hydrochloride, 1-(1-Adamantyl)-2-(*N*-methyl-4-anisidinyl)ethanone hydrochloride, *N*-(1-Adamantyl)-7-trifluoromethylquinoline-3-carboxamide, *N*-(1-Adamantyl)-2-(1-piperizinyl)quinoxaline-3-carboxamide, *N*-(1-Adamantyl)-2-(2-

- 51 -

aminoethylamino)quinoxaline-3-carboxamide, Methyl *N*-(3-quinolyl)-3-carboxyadamantane-1-carboxamide, 1-(1-Adamantyl)-2-[(*R*)-1-(1-naphthyl)ethan-1-ylamino]ethanone, *N*-(1-Adamantyl)-2-methoxyquinoxaline-3-carboxamide, Ethyl *N*-(1-adamantyl)-2-(3-propanoylamino)quinoxaline-3-carboxamide, *N*-(4-Chlorophenyl)-2, 3-dimethylquinoxaline-6-carboxamide, *N*-(1-Adamantyl)-6, 7-dimethylquinoxaline-2-carboxamide, *N*-[(*S*)-1-Tetralinyl]-2-quinoxalinecarboxamide, *N*-(4-Chlorophenethyl)-2-quinoxalinecarboxamide, *N*-(6-Quinolyl)-2-quinoxalinecarboxamide, *N*-(1-Tetralinmethyl)-2-quinoxalinecarboxamide, *N*-(1-Indanmethyl)-2-quinoxalinecarboxamide, *N*-(4, 4-Dimethylcyclohexyl)-2-quinoxalinecarboxamide, and pharmaceutically acceptable salts thereof.

Figure 1

1/10

1		18	
2		19	
3		20	
4		21	
5		22	
6		23	
7		24	
8		25	
9		26	
10		27	
11		28	
12		29	
13		30	
14		31	
15		32	
16		33	
17			

Figure 1 (continued)

34		51	
35		52	
36		53	
37		54	
38		55	
39		56	
40		57	
41		58	
42		59	
43		60	
44		61	
45		62	
46		63	
47		64	
48		65	
49		66	
50		67	
		68	

Figure 1 (continued)

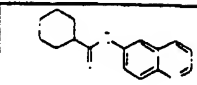
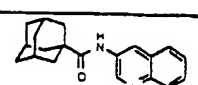
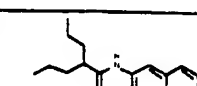
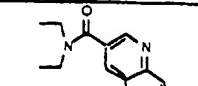
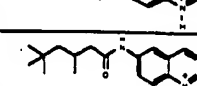
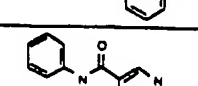
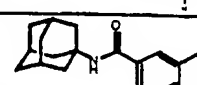

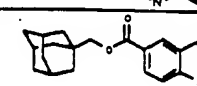
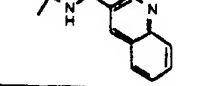
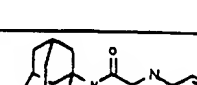
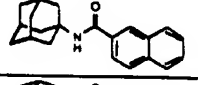
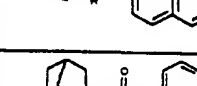
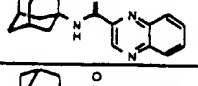

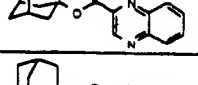
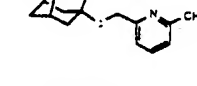
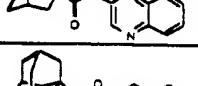
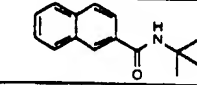
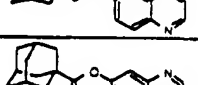
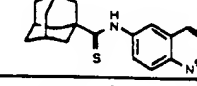
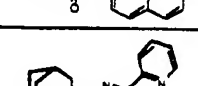
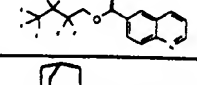

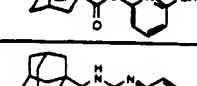
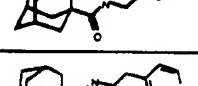
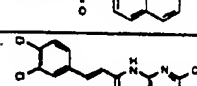
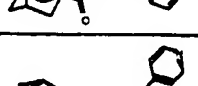
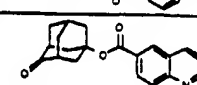
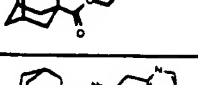
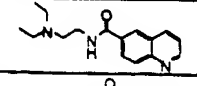
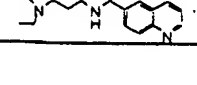
69		86	
70		87	
71		88	
72		89	
73		90	
74		91	
75		92	
76		93	
77		94	
78		95	
79		96	
80		97	
81		98	
82		99	
83		100	
84			
85			

Figure 1 (continued)

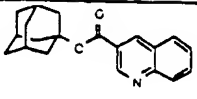
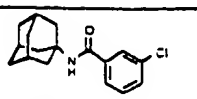
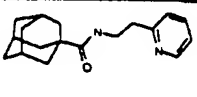
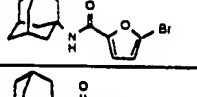
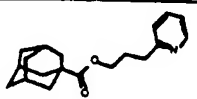
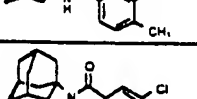
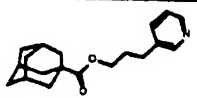
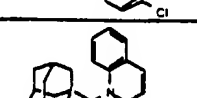
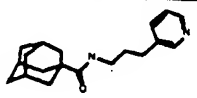
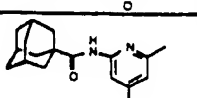
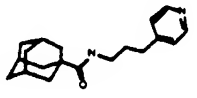
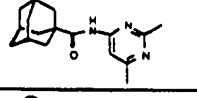
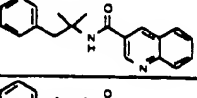
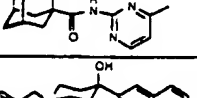
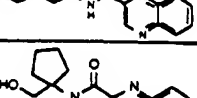
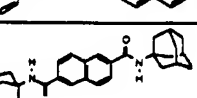
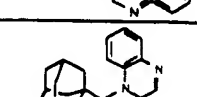
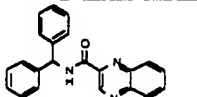
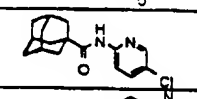
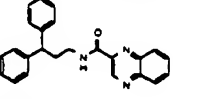
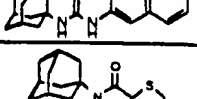
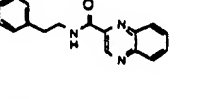
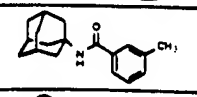
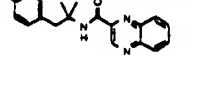
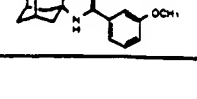
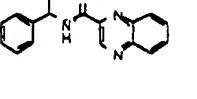




101		116	
102		117	
103		118	
104		119	
105		120	
106		121	
107		122	
108		123	
109		124	
110		125	
111		126	
112		127	
113		128	
114		129	
115		130	

Figure 1 (continued)

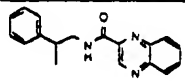
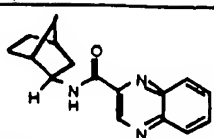
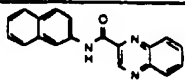
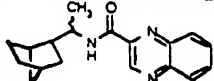
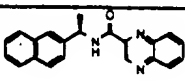
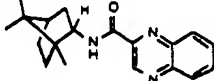
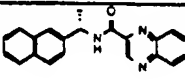
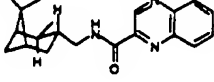
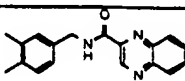
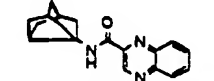
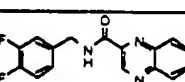
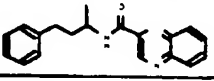
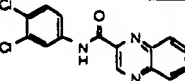
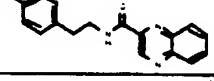
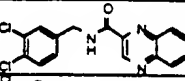
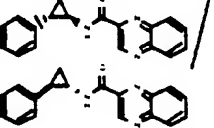
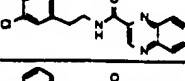
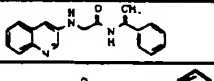
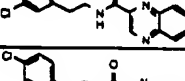
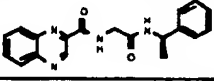
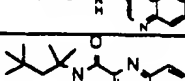
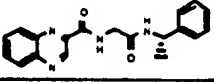
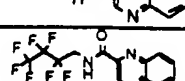
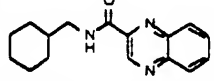
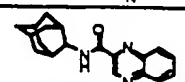
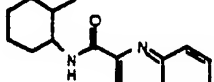
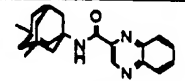
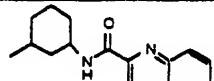
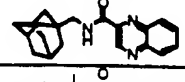
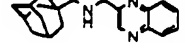

131		148	
132		149	
133		150	
134		151	
135		152	
136		153	
137		154	
138		155	
139		156	
140		157	
141		158	
142		159	
143		160	
144		161	
145			
146			
147			

Figure 1 (continued)

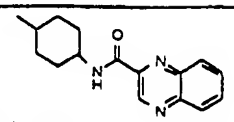
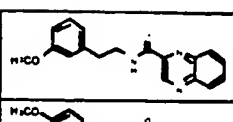
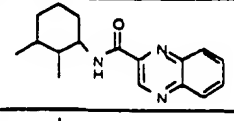
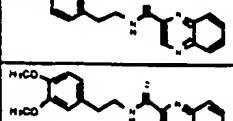
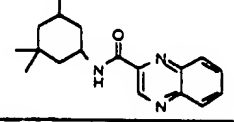
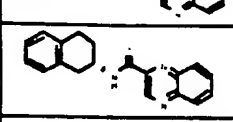
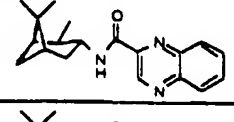
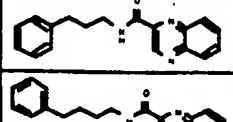
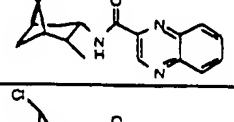
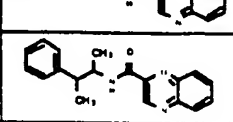
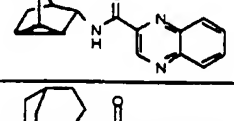
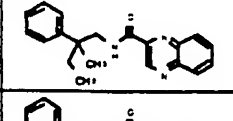
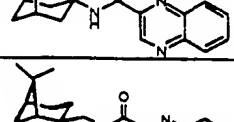
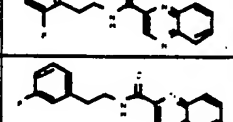

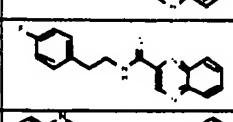
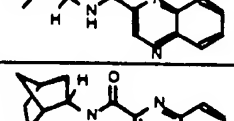
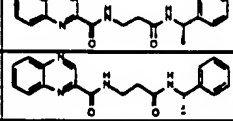
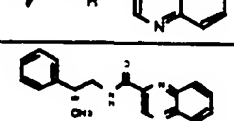
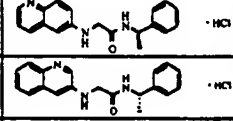
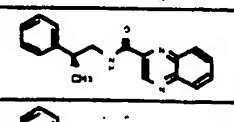
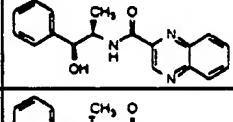
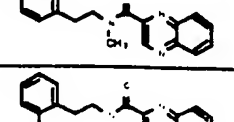
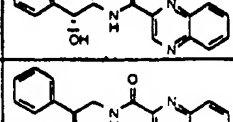
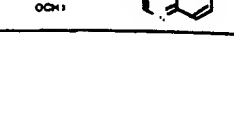
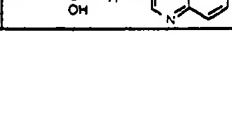



162		176	
163		177	
164		178	
165		179	
166		180	
167		181	
168		182	
169		183	
170		184	
171		185	
172		186	
173		187	
174		188	
175		189	
		190	
		191	
		192	
		193	

Figure 1 (continued)

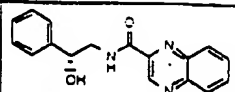
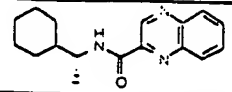
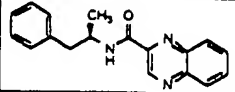
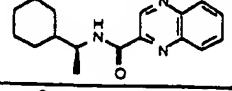
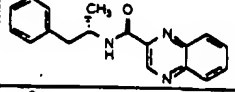
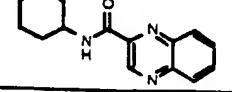
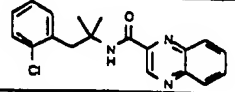
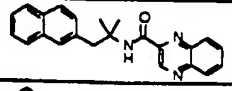
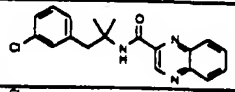
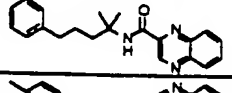
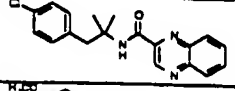
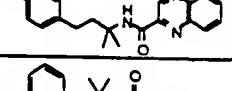
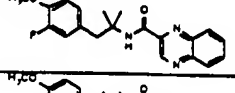
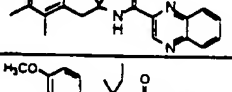
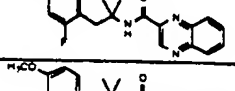
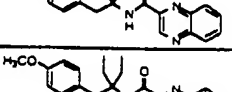
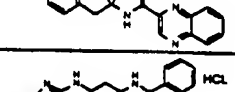
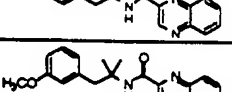
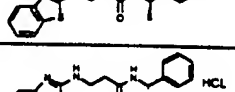
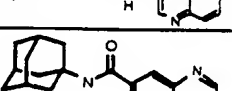
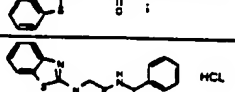
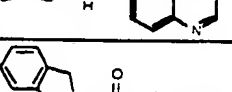
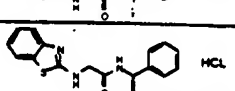
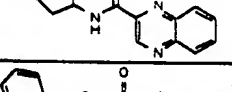
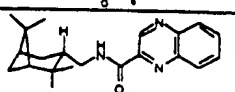
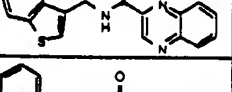
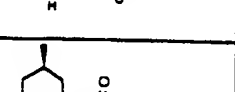
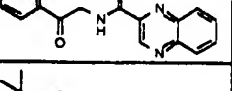
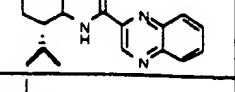
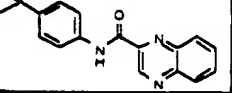
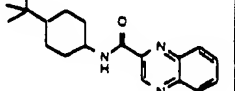
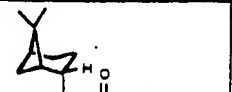
194		210	
195		211	
196		212	
197		213	
198		214	
199		215	
200		216	
201		217	
202		218	
203		219	
204		220	
205		221	
206		222	
207		223	
208		224	
209		225	

Figure 1 (continued)

8/10

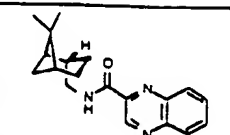
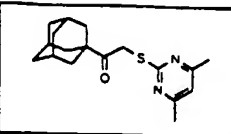
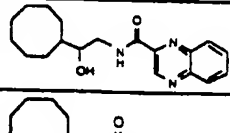
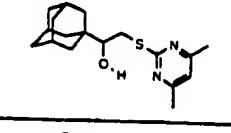
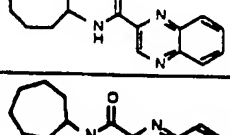
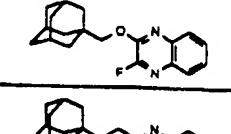
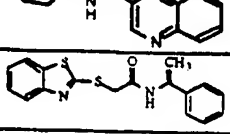
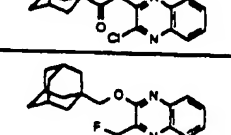
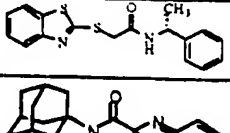
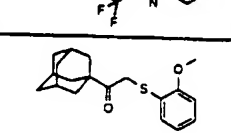
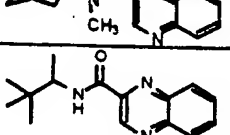
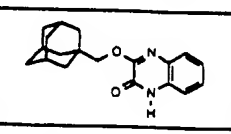
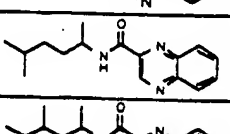
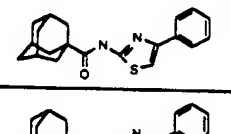
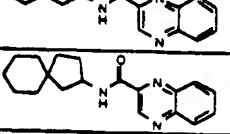
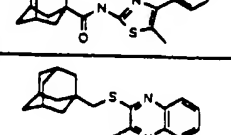
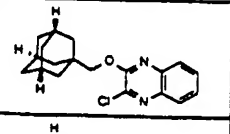
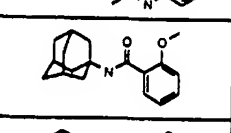
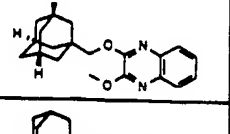
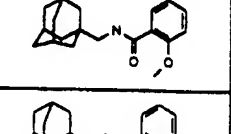
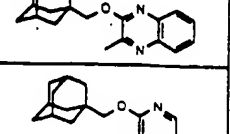
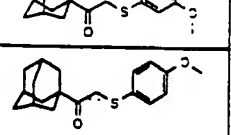
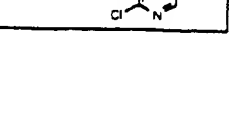





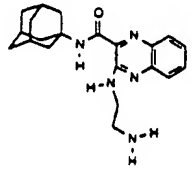
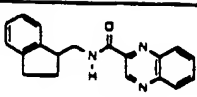
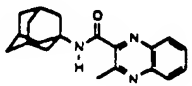
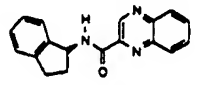
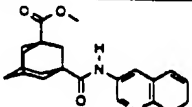
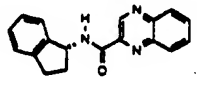
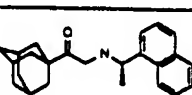
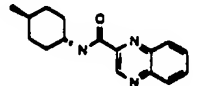
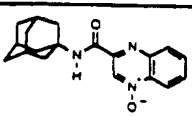
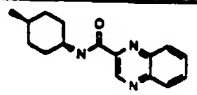
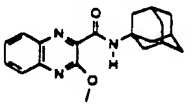
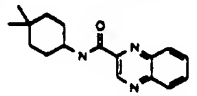
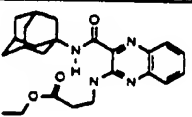
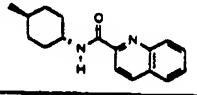
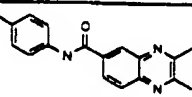
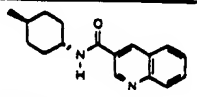
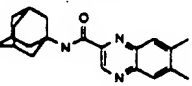
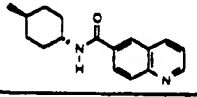
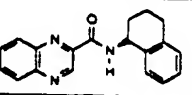
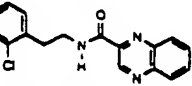
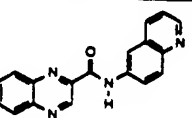
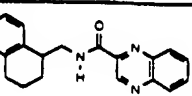
226		241	
227		242	
228		243	
229		244	
230		245	
231		246	
232		247	
233		248	
234		249	
235		250	
236		251	
237		252	
238		253	
239		254	
240			

Figure 1 (continued)

255.		270	
256		271	
257		272	
258		273	
259		274	
260		275	
261		276	
262		277	
263		278	
264		279	
265		280	
266		281	
267		282	
268			
269			

Figure 1 (continued)

283..		296	
284		297	
285		298	
286		299	
287		300	
288		301	
289		302	
290		303	
291		304	
292			
293			
294			
295			



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : C07D 215/38, 241/44, 277/72, A61K 31/47, 31/495, 31/425</p>	A3	<p>(11) International Publication Number: WO 99/26927</p> <p>(43) International Publication Date: 3 June 1999 (03.06.99)</p>																																																																				
<p>(21) International Application Number: PCT/US98/24833</p> <p>(22) International Filing Date: 20 November 1998 (20.11.98)</p> <p>(30) Priority Data: 60/066,758 21 November 1997 (21.11.97) US</p> <p>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/066,758 (CIP) Filed on 21 November 1997 (21.11.97)</p> <p>(71) Applicant (for all designated States except US): NPS PHARMACEUTICALS, INC. [US/US]; 420 Chipeta Way, Salt Lake City, UT 84108 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): VAN WAGENEN, Bradford, C. [US/US]; 3969 South 3250 East, Salt Lake City, UT 84124 (US). MOE, Scott, T. [US/US]; 6152 South Vinefield Lane, Salt Lake City, UT 84121 (US). SMITH, Daryl, L. [US/US]; 1592 East Parkridge Drive, Salt Lake City, UT 84121 (US). SHEEHAN, Susan, M. [US/US]; 1803 East Redondo Avenue, Salt Lake City, UT 84108 (US). SHCHERBAKOVA, Irina [RU/US]; 150 East First Avenue, Salt Lake City, UT 84103 (US). TRAVATO, Richard [US/US]; 4636 South 3075 East, Salt Lake City, UT 84117</p>																																																																						
<p>(US). WALTON, Ruth [US/US]; 1348 Country Hills Drive, Ogden, UT 84403 (US). BARMORE, Robert [US/US]; 1172 East Sunnyside Avenue, Salt Lake City, UT 84102 (US). DELMAR, Eric, G. [US/US]; 2967 East St. Mary's Circle, Salt Lake City, UT 84108 (US). STORMANN, Thomas, M. [US/US]; 1327 East Harrison, Salt Lake City, UT 84105 (US).</p> <p>(74) Agents: BENT, Stephen, A. et al.; Foley & Lardner, Suite 500, 3000 K Street, N.W., Washington, DC 20007-5109 (US).</p> <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p>																																																																						
<p>Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>																																																																						
<p>(88) Date of publication of the international search report: 21 October 1999 (21.10.99)</p>																																																																						
<p>(54) Title: METABOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS FOR TREATING CENTRAL NERVOUS SYSTEM DISEASES</p>																																																																						
<p>(57) Abstract</p> <p>The present invention provides compounds, and pharmaceutical compositions containing those compounds, that act as antagonists at metabotropic glutamate receptors. The compounds are useful for treating neurological diseases and disorders. Methods of preparing the compounds also are disclosed.</p>																																																																						
<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 15%;">1 ..</td> <td style="width: 35%;"></td> <td style="width: 15%;">18</td> <td style="width: 35%;"></td> </tr> <tr> <td>2</td> <td></td> <td>19</td> <td></td> </tr> <tr> <td>3</td> <td></td> <td>20</td> <td></td> </tr> <tr> <td>4</td> <td></td> <td>21</td> <td></td> </tr> <tr> <td>5</td> <td></td> <td>22</td> <td></td> </tr> <tr> <td>6</td> <td></td> <td>23</td> <td></td> </tr> <tr> <td>7</td> <td></td> <td>24</td> <td></td> </tr> <tr> <td>8</td> <td></td> <td>25</td> <td></td> </tr> <tr> <td>9</td> <td></td> <td>26</td> <td></td> </tr> <tr> <td>10</td> <td></td> <td>27</td> <td></td> </tr> <tr> <td>11</td> <td></td> <td>28</td> <td></td> </tr> <tr> <td>12</td> <td></td> <td>29</td> <td></td> </tr> <tr> <td>13</td> <td></td> <td>30</td> <td></td> </tr> <tr> <td>14</td> <td></td> <td>31</td> <td></td> </tr> <tr> <td>15</td> <td></td> <td>32</td> <td></td> </tr> <tr> <td>16</td> <td></td> <td>33</td> <td></td> </tr> <tr> <td>17</td> <td></td> <td></td> <td></td> </tr> </table>			1 ..		18		2		19		3		20		4		21		5		22		6		23		7		24		8		25		9		26		10		27		11		28		12		29		13		30		14		31		15		32		16		33		17			
1 ..		18																																																																				
2		19																																																																				
3		20																																																																				
4		21																																																																				
5		22																																																																				
6		23																																																																				
7		24																																																																				
8		25																																																																				
9		26																																																																				
10		27																																																																				
11		28																																																																				
12		29																																																																				
13		30																																																																				
14		31																																																																				
15		32																																																																				
16		33																																																																				
17																																																																						

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/24833

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D215/38 C07D241/44 C07D277/72 A61K31/47 A61K31/495
A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 05818 A (NPS PHARMACEUTICALS, INC.) 29 February 1996 (1996-02-29) claims 1-41; figures 1A-1N ---	1-3,13, 15-17
X	B. PRAGER ET AL.: "Beilsteins Handbuch der Organischen Chemie, 9. Bd." 1926, VERLAG VON JULIUS SPRINGER, BERLIN XP002101990 * Benzoessäurecyclohexylester, Benzoessäure-[2-methylcyclohexyl]-ester, Benzoessäure-[3-methylcyclohexyl]-ester page 114 --- -/-	1-4

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

5 May 1999

Date of mailing of the international search report

03. 09. 99

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Herz, C

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/24833

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	B. PRAGER ET AL.: "Beilsteins Handbuch der Organischen Chemie, 12. Bd." 1929, VERLAG VON JULIUS SPRINGER, BERLIN XP002101991 * Propionylamino-cyclohexan, Benzamino-cyclohexan * page 7 ---	1-4
X	H.-G. BOIT: "Beilsteins Handbuch der Organischen Chemie" 1970, SPRINGER-VERLAG, BERLIN XP002101992 * Thiobenzoesäure-S-cyclohexylester, 2-Benzoylmercapto-bornan * page 1964 ---	1-4
X	R. LUCKENBACH: "Beilsteins Handbuch der Organischen Chemie, 3. u. 4. Eg., 22. Bd." 1979, SPRINGER-VERLAG, BERLIN XP002101993 * Nicotinsäure-cyclohexylamid * page 398 ---	11
X	EP 0 407 192 A (MEIJI SEIKA K. K.) 9 January 1991 (1991-01-09) * Compound no. 29 * claim 1 ---	1-4,6, 13,14
X	US 3 632 581 A (J. R. POTOSKI, M. E. FREED) 4 January 1972 (1972-01-04) claims 1,121-4,6,13,14; example VIII ---	1-4,6, 13,14
X	DE 20 50 074 A (E. R. SQUIBB & SONS, INC.) 6 May 1971 (1971-05-06) examples 1,2 ---	1-4,6, 13,14
X	DE 27 28 248 A (LABORATOIRES DEBAT) 5 January 1978 (1978-01-05) claim 5; example 24 ---	1-4,6, 13,14
X	WO 96 40641 A (TANABE SEIYAKU CO., LTD.) 19 December 1996 (1996-12-19) * entire document * ---	1-4,6, 13,14
X	EP 0 002 066 A (TEVA PHARMACEUTICAL INDUSTRIES LTD.) 30 May 1979 (1979-05-30) claims 1,40 ---	1-4,6, 13,14
X	PATENT ABSTRACTS OF JAPAN vol. 095, no. 010, 30 November 1995 (1995-11-30) & JP 07 179371 A (CANON INC.), 18 July 1995 (1995-07-18) abstract ---	1-4,6, 13,14

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/24833

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	G. FENECH ET AL.: "Derivati amidici dell'acido 1-adamantancarbossilico a potenziale attivita antivirale ed antitumorale" BOLL. CHIM. FARM., vol. 118, no. 2, 1979, pages 78-87, XP002101981 example 11	1-4,6, 13,14
X	--- S. S. SABRI ET AL.: "Syntheses and Antibacterial Activity of Some New N-(3-Methyl-2-quinoxalyl) Amino Alcohols and Amine 1,4-Dioxides" J. CHEM. ENG. DATA, vol. 29, no. 2, 1984, pages 229-231, XP002101982 * Scheme I *	1-4,6, 13,14
X	--- F. HONG ET AL.: "Design, synthesis and pharmacological test of a quinoline based, nonpeptidic analogue of neurotensin(8-13)" J. CHEM. SOC., PERKIN TRANS. 1, vol. 14, 1997, pages 2083-2088, XP002101983 * Scheme 3 *	1-4,6, 13,14
X	--- M. ZANISI ET AL.: "Excitatory amino acids as modulators of gonadotropin secretion" AMINO ACIDS, vol. 6, no. 1, 1994, pages 47-56, XP002101984 page 53 - page 55	1
X	--- H. ZIMMER, H. D. BENSON: "Kondensierte Imidazole; Versuche zur Synthese des 13,16- und 14,16-Diazasterin-Gerüstes" CHIMIA, vol. 26, no. 3, 1972, pages 131-133, XP002101985 tables 1-4	1-4,6, 13,14
X	--- F. SZTARICKSKAI ET AL.: "Synthese und virushemmende in-vitro-Wirkung neuerer 1-substituierter Adamantanderivate" PHARMAZIE, vol. 30, no. 9, 1975, pages 571-581, XP002101986 tables 3,5,6 --- -/--	1-4,6, 13,14

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/24833

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>N. G. KOZLOV, G. P. KOROTISHOVA: "Synthesis of 1-(1-adamantyl)-2,3-dihydroxy-3-R-1-propan ones" ZH. OBSHCH. KHIM., vol. 66, no. 12, 1996, pages 2039-2041, XP002101987 * Compounds of formula X, XII *</p>	1-4,6, 13,14
X	<p>K. H. KIM ET AL.: "Quantitative Structure-Activity Relationship in 1-Aryl-2-(alkylamino)ethanol Antimalarials" J. MED. CHEM., vol. 22, no. 4, 1979, pages 366-391, XP002101988 table II</p>	1-4,6, 13,14
X	<p>L. C. MARCH ET AL.: "Antimalarials. 2. Dihydro-1,3-oxazinoquinolines and Dihydro-1,3-pyridobenzoxazines" J. MED. CHEM., vol. 16, no. 4, 1973, pages 337-342, XP002101989 example 55</p>	1-4,6, 13,14
X	<p>CHEMICAL ABSTRACTS, vol. 115, no. 7, 19 August 1991 (1991-08-19) Columbus, Ohio, US; abstract no. 70978a, N. S. KOZLOV ET AL.: "Synthesis of adamantane-type beta-amino ketones" page 733; XP002101994 abstract & VESTSI AKAD. NAVUK BSSR, SER. KHIM. NAVUK, no. 1, 1991, pages 60-65,</p>	1-4,6, 13,14

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 24833

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

5-10 (all partial),13-21 (all partial),23,24-27 (all partial)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 98/24833

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 5-10 (all partial), 13-21 (all partial), 23,
24-27 (all partial)

Compounds containing azanaphthalene and adamantane moieties

2. Claims: 5-10 (all partial), 13-19 (all partial), 21

Compounds containing azanaphthalene and pinane moieties

3. Claims: 5-10 (all partial), 13-21 (all partial), 23,
24-27 (all partial)

Compounds containing azanaphthalene and norbornane moieties

4. Claims: 5-10 (all partial), 13-21 (all partial), 23,
24-27 (all partial)

Compounds containing azanaphthalene and bornane moieties

5. Claims: 5-10 (all partial), 13-21 (all partial), 23,
24-27 (all partial)

Compounds containing azanaphthalene and noradamantane
moieties

6. Claims: 5-10 (all partial), 13-21 (all partial), 23,
24-27 (all partial)

Compounds containing azanaphthalene and isopinocamphe
moieties

7. Claims: 5-10 (all partial), 13-21 (all partial), 23,
24-27 (all partial)

Compounds containing azanaphthalene and tricycloheptane
moieties

8. Claims: 5-10 (all partial), 13-21 (all partial), 23,
24-27 (all partial)

Compounds containing azanaphthalene and tricycloundecane

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 98/24833

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

moieties

9. Claims: 5-10 (all partial), 13-21 (all partial), 23,
24-27 (all partial)

Compounds containing azanaphthalene and myrtane moieties

10. Claims: 5-10 (all partial), 13-21 (all partial), 23,
24-27 (all partial)

Compounds containing azanaphthalene and isobornane moieties

11. Claims: 5-10 (all partial), 13-21 (all partial), 23,
24-27 (all partial)

Compounds containing azanaphthalene and phenylalkyl moieties

12. Claims: 5-10 (all partial), 13-21 (all partial), 23,
24-27 (all partial)

Compounds containing azanaphthalene and indane moieties

13. Claims: 5-10 (all partial), 13-21 (all partial), 23,
24-27 (all partial)

Compounds containing azanaphthalene and cycloalkyl moieties

14. Claims: 5-10 (all partial), 13-21 (all partial), 23,
24-27 (all partial)

Compounds containing azanaphthalene and haloalkyl moieties

15. Claims: 12-17 (all part), 25 (part)

Compounds containing benzothiazolyl and adamantyl moieties

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/24833

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9605818 A	29-02-1996	AU 3414295 A	14-03-1996
EP 407192 A	09-01-1991	CA 2020667 A	08-01-1991
		DE 69030030 D	10-04-1997
		DE 69030030 T	26-06-1997
		EP 0669321 A	30-08-1995
		JP 2633377 B	23-07-1997
		JP 3128355 A	31-05-1991
		KR 134084 B	22-04-1998
		US 5190952 A	02-03-1993
US 3632581 A	04-01-1972	NONE	
DE 2050074 A	06-05-1971	CH 525888 A	31-07-1972
		CH 530400 A	15-11-1972
		FR 2070165 A	10-09-1971
		GB 1329447 A	05-09-1973
DE 2728248 A	05-01-1978	BE 855851 A	20-12-1977
		FR 2355829 A	20-01-1978
		ZA 7703797 A	30-05-1978
WO 9640641 A	19-12-1996	US 5707985 A	13-01-1998
		AU 6274396 A	30-12-1996
EP 2066 A	30-05-1979	AU 4184378 A	31-05-1979
		CA 1119170 A	02-03-1982
		IT 1101419 B	28-09-1985
		JP 54088249 A	13-07-1979
		US 4254128 A	03-03-1981
		ZA 7806543 A	31-10-1979
JP 07179371 A	18-07-1995	NONE	

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.